ANNUAL REPORT
OF
PROGRAM ACTIVITIES
NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

FISCAL YEAR 1981

VOLUME I

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service National Institutes of Health

ANNUAL REPORT

OF

PROGRAM ACTIVITIES

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

oc

FISCAL YEAR 1981

VOLUME I

P
Soc
4278
1902
v 1

ANNUAL REPORT

October 1, 1980 through September 30, 1981

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents*

VOLUME I — TAB

OFFICE OF THE DIRECTOR, NINCDS (OD) 1
DIRECTOR (Acting): Dr. Murray Goldstein
DEPUTY DIRECTOR (Acting): Dr. Katherine L. Bick

EXECUTIVE OFFICER: Mr. Richard L. Sherbert, Jr.

EQUAL EMPLOYMENT OPPORTUNITY OFFICE (EEO)
Coordinator: Mr. Levon O. Parker

OFFICE OF SCIENTIFIC AND HEALTH REPORTS (OSHR)
Chief: Ms. Sylvia Shaffer

OFFICE OF PLANNING AND ANALYSIS (OPA)
Chief: Mr. LeRoy Goldman
Deputy Chief: Mr. Joseph Culhane
Senior Medical Advisor: Dr. Zekin A. Shakhashiri

OFFICE OF BIOMETRY AND FIELD STUDIES (OBFS) 1.A
Chief: Mr. William Weiss
Associate Chief: Mr. Bernard H. Kroll

EXTRAMURAL ACTIVITIES PROGRAM (EAP) 2
DIRECTOR: Dr. John C. Dalton
DEPUTY DIRECTOR: Dr. John W. Diggs

COMMUNICATIVE DISORDERS PROGRAM (CDP) 3
DIRECTOR: Dr. Ralph F. Naunton
DEPUTY DIRECTOR: Dr. J. Buckminster Ranney

FUNDAMENTAL NEUROSCIENCES PROGRAM (FNP) 4
DIRECTOR: Dr. Eugene Streicher
DEPUTY DIRECTOR: Dr. W. Watson Alberts

NEUROLOGICAL DISORDERS PROGRAM (NDP) 5
DIRECTOR: Dr. Floyd J. Brinley, Jr
DEPUTY DIRECTOR (Acting): Dr. Eugene J. Oliver

EPILEPSY BRANCH (EB) 5.A
Chief: Dr. Roger J. Porter

DEVELOPMENTAL NEUROLOGY BRANCH (DNB) 5.B
Chief: Dr. Joseph S. Drage

STROKE AND TRAUMA PROGRAM (STP) 6
DIRECTOR: Dr. Michael D. Walker

VOLUME II** TAB

OFFICE OF THE DIRECTOR OF INTRAMURAL RESEARCH (ODIR) 7
DIRECTOR: Dr. Thomas N. Chase

LABORATORY DIRECTOR: Dr. Richard L. Irwin

INSTRUMENTATION AND COMPUTERS SECTION (ICS) 7.A
Chief: Dr. Theodore R. Colburn

NEUROEPIDEMIOLOGY SECTION (NES) 7.B
Chief: Dr. Bruce S. Schoenberg

NEUROTOXICOLOGY SECTION (NTS) 7.C
Chief: Dr. Ellen K. Silbergeld

LABORATORY OF CENTRAL NERVOUS SYSTEM STUDIES (LCNSS) 10
CHIEF: Dr. D. Carleton Gajdusek
DEPUTY: Dr. Clarence J. Gibbs, Jr.

LABORATORY OF NEUROPATHOLOGY AND NEUROANATOMICAL SCIENCES (LNNS) 13
CHIEF: Dr. Igor Klatzo

LABORATORY OF NEURAL CONTROL (LNLC) 14
CHIEF: Dr. Robert E. Burke

LABORATORY OF NEUROPHYSIOLOGY (LNP) 15
CHIEF: Dr. Jeffery Barker

LABORATORY OF BIOPHYSICS (LB) 16
CHIEF: Dr. William J. Adelman, Jr.

LABORATORY OF NEUROCHEMISTRY (LNC) 17
CHIEF: Dr. Janet Passonneau

LABORATORY OF MOLECULAR BIOLOGY (LMB) 18
CHIEF: Dr. Ernst Freese

LABORATORY OF NEURO-OTOLARYNGOLOGY (LNO) 19
CHIEF: Dr. Jorgen Fex

LABORATORY OF MOLECULAR GENETICS (LMG) 23
CHIEF (Acting): Dr. Robert A. Lazzarini

LABORATORY OF EXPERIMENTAL NEUROLOGY 24
CHIEF: Dr. William F. Caveness

VOLUME II* (Cont'd) TAB

CLINICAL DIRECTOR: Dr. Donald B. Calne

MEDICAL NEUROLOGY BRANCH (MNB) 8
CHIEF (Acting): Dr. John L. Sever

SURGICAL NEUROLOGY BRANCH (SNB) 9
CHIEF: Dr. Paul L. Kornblith

CLINICAL NEUROSCIENCES BRANCH (CNB) 11
CHIEF (Acting): Dr. Susumo Sato

DEVELOPMENTAL METABOLIC NEUROLOGY BRANCH (DMNB) 12
CHIEF: Dr. Roscoe O. Brady

INFECTIOUS DISEASES BRANCH (IDB) 20
CHIEF: Dr. John L. Sever

EXPERIMENTAL THERAPEUTICS BRANCH (ETB) 21
CHIEF: Dr. Donald B. Calne

NEUROIMMUNOLOGY BRANCH (NIB) 22
CHIEF: Dr. Dale E. McFarlin

LABORATORY OF MOLECULAR GENETICS (LMG) 23
CHIEF (Acting): Dr. Robert A. Lazzarini

LABORATORY OF EXPERIMENTAL NEUROLOGY 24
CHIEF: Dr. William F. Caveness

Alphabetical Listing of NINCDS PRINCIPAL INVESTIGATORS page iv
Numerical Listing of NINCDS Research Projects page vi

---

* A detailed Table of Contents for each program area will be found immediately following the TAB indicator.

** In this section of the Table of Contents (Intramural Research Program), the Laboratories and the Branches are grouped according to their Basic Science or Clinical Research functions respectively. However, the arrangement in the text of the Annual Report follows the official sequential order.

ANNUAL REPORT
October 1, 1980 through September 30, 1981
National Institute of Neurological and Communicative Disorders and Stroke

Alphabetical Listing of NINCDS Principal Investigators

NAME	TAB	PAGES	NAME	TAB	PAGES
Abe, T	13	42	Edelstein, S	1.A	45,57
Adelman, W J Jr	16	9,13,17	Ehrenstein, G	16	31,40
Albers, R W	17	11,45	Eldridge, R	1.A	93
Ali, M A	15	26	Eldridge, R	7.B	21,24,27
Alkon, D L	16	24	Elkins, E	3	61,73
Altschuler R A	19	3,8	Ellenberg, J H	1.A	91,95,97,99
Anders, J J	13	62	Ellenberg, J H	1.A	109,123,131
Anderson, D W	1.A	75,79,81	Ellenberg, J.H	1.A	137,140
Anderson, D W	7.B	53	Ellenberg, J H	5.B	28,31,53
Asher, D M	10	28	Engel, W K	8	1,2,3,5
Askanas, V	8	3	Fedio, P	11	6,9,11,13
Bajda, L	5	4	Feinberg, R	5.B	39
Bak, M J	14	15	Fex, J	19	3,8
Barker, J L	15	3,16	Fishman, I G	1.A	51,53
Barranger, J A	12	9,51,55,63	Fishman, P H	12	19,47
Baum, H M	1.A	65,71,73	FitzHugh, R	16	33
Baum, H M	1.A	77,83,85	Freese, E	18	6,13,17
Beane, W	15	31	Fujiwara, K	13	25
Bellini, W J	22	10	Gajdusek, D C	10	28,33
Blasberg, R G	9	61	Gal, A E	12	23,43,45
Brady, R O	12	15,63	Garruto, R M	10	28
Brightman, M W	13	66	Gibbs, C J	10	28,33
Broman, S H	5.B	27,37,40,50	Gilbert, D L	16	35
Brooks, R A	1.A	103,107	Goldstein, M	1.A	27,32,37
Brooks, R A	1.A	113,115	Goldstein, M	1.A	39,71
Brooks, R A	9	56,60	Gravell, M	20	27
Brouwers, P	11	6,9,11	Gross, C	1.A	43,47,49
Brown, P W	10	28	Gross, C	1.A	55,59
Bruckner, A	1.A	117	Gulley, R L	19	3,8
Burke, R E	14	8,37	Hara, K	15	26
Calne, D B	1.A	89,105,111	Harper, J S III	20	40,47
Calne, D B	21	10	Hawkins, N	1.A	61
Cammermeyer, J	13	68,70,72	Henneberry, R C	18	17,21
Caspary, W J	1.A	129	Hirtz, D G	1.A	91,123
Caveness, W F	24	1,2	Hirtz, D G	5.B	28,53
Cervetto, L	15	31	Hoffman, D W	19	3
Chase, T N	9	60	Houff, S A	20	23,50
Chase, T N	21	16	Howell, W L	1.A	31
Chen, T C	1.A	31,32,33,35	Hruska, R E	7.C	88
Chen, T C	1.A	37,39,63	Jane, J	1.A	29
Constantopoulos, G	12	59	Johnston, G S	9	61
Dambrosia, J	1.A	55,89,93,95	Jokl, P	1.A	27
Dambrosia, J	1.A	101,111,131	Jones, A E	9	61
Dambrosia, J	1.A	133,135	Karniouchina, I	13	46
DeLaPaz, R L	9	60	Kase, C	1.A	49,55,135
DiChiro, G	9	47,49,53	Kebabian, J W	21	32
DiChiro, G	9	56,60	Kessler, R M	9	61
Dickson, J W	19	8	Kirino, T	13	64
Drage, J S	5.B	34,49	Klatzo, I	13	8,22
Dubois-Dalcq, M	20	53	Kornblith, P L	9	13,38,42,60

Alphabetical Listing of NINCDS Principal Investigators - (Cont'd)

NAME	TAB	PAGES
Kudrjavcev, T	7.B	36,41
Kunitz, S C	1.A	51,53,55
Kunitz, S C	1.A	59,67,69
Kupferberg, H J	5.A	23
Lange, G D	15	26
Larsen, A	21	10
Larson, S	9	61
Lasansky, A	15	31
Lazzarini, R A	23	4
Lecar, H	16	42
Lee, Y J	1.A	87,91,119
Lee, Y J	1.A	125,127
Lee, Y J	1.A	129,131
LeWitt, P	1.A	89,111
LeWitt, P	21	10
Li, C L	9	66
Loeb, G E	14	31
Lohr, J	15	31
London, W T	1.A	31,146
London, W T	20	40,44,47,50
Ludlow, C	1.A	65,121,125
Ludlow, C	3	55,58,63,70
Lust, W D	17	20,38
MacNichol, E F	15	26
Madden, D L	20	13,18
Marchiafava, P L	15	19
Mariani, A	15	26
Marks, W B	14	26
Martin, A	11	6,11
Martin, M R	19	3,8
McAndrews, J F	1.A	27
McBurney, R N	15	28
McFarland, H F	22	4,21
McFarlin, D E	22	4,10,17
Mohr, J	1.A	49,55,135
Morgenthaler, D G	1.A	107
Morris, S J	7.C	80
Moscicki, E	1.A	65
Murray, M R	13	38
Myrianthopoulos, N C	5.B	42,51,56
Naylor, A F	5.B	58
Nelson, K B	1.A	91,99,101
Nelson, K B	1.A	123,137,140
Nelson, K B	5.B	28,31,53
Newmark, M E	9	60
Nichols, B	1.A	41
Nichols, P L	5.B	35
Nitsch, C	13	10,13,16
Palmer, A E	20	47
Passonneau, J V	17	17,30,34,42
Patronas, N J	9	60
Pikus, A	3	66,68,75,77
Pikus, A	3	79,81,83
Pikus, A	3	85,87,89
Poduslo, J F	22	10
Porro, M G	5.A	25
Porter, R J	1.A	140
Porter, R J	9	60
Porter, R J	21	22,27
Quarles, R H	12	35
Quindlen, E	9	60
Reddy, N B	8	3
Reese, T S	13	55,57
Reiner, B	1.A	121
Richardson, K	1.A	57
Rieth, K G	9	56
Sanes, J	1.A	89
Sank, V J	9	56,60
Sato, S	11	16,18,20
Schmidt, E M	14	20
Schnapf, J	15	28
Schoenberg, B S	7.B	30,33,36,39
Schoenberg, B S	7.B	41,44,46,48
Schoenberg, B S	7.B	51,53,55,57
Sever, J L	1.A	109
Sever, J L	20	13,23
Shakhashiri, Z A	1	- -
Silbergeld, E K	7.C	62,64
Simon, R	1.A	119
Smith, B H	9	38,60
Smith, T G	15	3
Sofijanov, N	1.A	123
Spatz, M	13	27,28,29,30
Spatz, M	13	32,35,40
Spatz, M	13	43,44,49
Suzuki, R	13	19
Talbert, A J	1.A	103,107,113
Talbert, A J	1.A	115,131
Tandon, P	1.A	29
Taylor, R E	16	38
Trams, E G	12	27,31
Wagner, H G	15	19,21,23,26
Wallen, W C	20	31,37
Walters, J R	21	38
Ward, C	1.A	93
Ward, C	21	10
Webster, H deF	13	51
Weinfeld, F D	1.A	63,73,79,81
Weiss, G H	1.A	113
Weiss, W	1.A	27,29,59
Wells, J B	16	20,23
Wenthold, R J	19	3,8
Wilmes, F	13	9
Wolbarsht, M H	15	26
Wolf, A P	9	61
Wolf, P	1.A	133
Zalewski, A A	17	14,25

ANNUAL REPORT

October 1, 1980 through September 30, 1981

National Institute of Neurological and Communicative Disorders and Stroke
INTRAMURAL RESEARCH PROJECTS

Numerical Listing

PROJECT NUMBER	TAB	PAGE
Z01 NS 00200-27 CN	11	6
Z01 NS 00402-25 ID	20	13
Z01 NS 00706-22 DMN	12	9
Z01 NS 00813-20 LNC	17	11
Z01 NS 00815-21 DMN	12	15
Z01 NS 00969-17 CNSS	10	33
Z01 NS 00972-10 ID	20	40
Z01 NS 01034-19 MN	8	3
Z01 NS 01039-19 MN	8	5
Z01 NS 01047-19 SN	9	47
Z01 NS 01163-19 NDP	5	4
Z01 NS 01189-13 MN	8	1
Z01 NS 01190-17 MN	8	2
Z01 NS 01195-17 SN	9	49
Z01 NS 01244-17 LMB	18	6
Z01 NS 01245-16 CN	11	9
Z01 NS 01274-17 DNB	5.B	58
Z01 NS 01282-17 CNSS	10	28
Z01 NS 01309-16 DMN	12	19
Z01 NS 01424-15 CN	11	11
Z01 NS 01442-15 LNNS	13	55
Z01 NS 01457-15 DMN	12	23
Z01 NS 01480-14 DMN	12	27
Z01 NS 01481-14 DMN	12	31
Z01 NS 01586-14 LNC	17	14
Z01 NS 01654-14 SN	9	53
Z01 NS 01658-14 CN	11	13
Z01 NS 01659-13 LNP	15	31
Z01 NS 01686-13 LNLC	14	8
Z01 NS 01687-13 LNLC	14	15
Z01 NS 01688-13 LNLC	14	20
Z01 NS 01731-13 ID	20	27
Z01 NS 01805-13 LNNS	13	62
Z01 NS 01808-12 DMN	12	35
Z01 NS 01857-12 DNB	5.B	27
Z01 NS 01881-11 LNNS	13	57
Z01 NS 01886-11 LMB	18	13
Z01 NS 01924-11 ODIR	7.B	21
Z01 NS 01927-11 ODIR	7.B	24
Z01 NS 01950-10 LB	16	9
Z01 NS 01983-10 ID	20	31
Z01 NS 01984-10 ID	20	37
Z01 NS 01985-10 ID	20	18
Z01 NS 01986-10 ID	20	44
Z01 NS 01995-09 LNNS	13	51
Z01 NS 01999-09 LNNS	13	27
Z01 NS 02000-09 LNNS	13	28
Z01 NS 02006-09 LNC	17	17
Z01 NS 02010-09 SN	9	66
Z01 NS 02019-09 LNP	15	3
Z01 NS 02026-09 LMG	23	4
Z01 NS 02034-09 ID	20	53
Z01 NS 02038-09 ID	20	23
Z01 NS 02058-09 DNB	5.B	28
Z01 NS 02059-09 DNB	5.B	31
Z01 NS 02060-09 DNB	5.B	34
Z01 NS 02062-09 DNB	5.B	35
Z01 NS 02073-08 SN	9	56
Z01 NS 02079-08 LNLC	14	26
Z01 NS 02080-08 LNLC	14	31
Z01 NS 02086-08 LNNS	13	64
Z01 NS 02087-08 LB	16	13
Z01 NS 02088-08 LB	16	31
Z01 NS 02091-08 LB	16	33
Z01 NS 02092-08 LB	16	17
Z01 NS 02106-08 DNB	5.B	37
Z01 NS 02107-08 DNB	5.B	39
Z01 NS 02108-08 DNB	5.B	40
Z01 NS 02109-08 DNB	5.B	42
Z01 NS 02112-08 DNB	5.B	49
Z01 NS 02114-08 OBFS	1.A	137
Z01 NS 02136-07 ID	20	47
Z01 NS 02139-07 ET	21	38
Z01 NS 02142-07 LNC	17	20
Z01 NS 02144-07 LNNS	13	66
Z01 NS 02151-07 LB	16	24
Z01 NS 02152-07 LNP	15	23
Z01 NS 02160-07 LNLC	14	37

Intramural Research Projects - Numerical Listing (Cont'd)

PROJECT NUMBER	TAB	PAGE	PROJECT NUMBER	TAB	PAGE
Z01 NS 02162-07 DMN	12	43	Z01 NS 02300-05 ODIR	7.B	44
Z01 NS 02163-07 DMN	12	45	Z01 NS 02301-05 ODIR	7.B	46
Z01 NS 02165-07 LNNS	13	29	Z01 NS 02305-05 ODIR	7.B	48
Z01 NS 02167-07 ODIR	7.B	27	Z01 NS 02307-05 ODIR	7.B	51
Z01 NS 02169-07 DNB	5.B	50	Z01 NS 02310-05 OBFS	1.A	33
Z01 NS 02171-07 DNB	5.B	51	Z01 NS 02312-05 OBFS	1.A	109
Z01 NS 02185-07 CDP	3	55	Z01 NS 02315-04 SN	9	60
Z01 NS 02189-06 LEN	24	1	Z01 NS 02316-04 LB	16	40
Z01 NS 02202-06 NI	22	4	Z01 NS 02317-04 LB	16	42
Z01 NS 02203-06 NI	22	10	Z01 NS 02318-04 ET	21	27
Z01 NS 02204-06 NI	22	17	Z01 NS 02319-04 ODIR	7.C	62
Z01 NS 02205-06 NI	22	21	Z01 NS 02324-04 LNNS	13	32
Z01 NS 02216-06 LNO	19	3	Z01 NS 02327-04 LNNS	13	35
Z01 NS 02217-06 LNO	19	8	Z01 NS 02328-04 LNNS	13	38
Z01 NS 02218-06 LB	16	35	Z01 NS 02329-04 LB	16	23
Z01 NS 02219-06 LB	16	38	Z01 NS 02330-04 LNP	15	16
Z01 NS 02221-06 LNP	15	28	Z01 NS 02331-04 LNP	15	19
Z01 NS 02234-06 DNB	5.B	53	Z01 NS 02332-04 DNB	5.B	56
Z01 NS 02236-06 ET	21	22	Z01 NS 02336-04 CDP	3	61
Z01 NS 02237-05 OBFS	1.A	79	Z01 NS 02337-04 CDP	3	63
Z01 NS 02238-05 OBFS	1.A	69	Z01 NS 02339-04 LNP	15	26
Z01 NS 02239-05 OBFS	1.A	81	Z01 NS 02340-04 OBFS	1.A	67
Z01 NS 02240-05 ODIR	7.B	30	Z01 NS 02341-04 OBFS	1.A	71
Z01 NS 02241-05 ODIR	7.B	33	Z01 NS 02342-04 OBFS	1.A	35
Z01 NS 02243-05 ODIR	7.B	36	Z01 NS 02354-04 OBFS	1.A	140
Z01 NS 02247-05 CDP	3	58	Z01 NS 02357-03 LNNS	13	40
Z01 NS 02254-05 LNC	17	25	Z01 NS 02358-03 LNNS	13	42
Z01 NS 02256-05 LNC	17	30	Z01 NS 02360-03 LNNS	13	43
Z01 NS 02257-05 LNC	17	38	Z01 NS 02361-04 LNNS	13	44
Z01 NS 02258-05 ET	21	10	Z01 NS 02362-03 LNNS	13	70
Z01 NS 02263-05 ET	21	32	Z01 NS 02364-03 LMB	18	17
Z01 NS 02264-05 ODIR	7.C	64	Z01 NS 02365-03 LMB	18	21
Z01 NS 02265-05 ET	21	16	Z01 NS 02366-03 DMN	12	47
Z01 NS 02269-05 CN	11	16	Z01 NS 02367-03 SN	9	13
Z01 NS 02271-05 ID	20	50	Z01 NS 02368-03 SN	9	38
Z01 NS 02273-05 LB	16	20	Z01 NS 02370-03 ODIR	7.B	53
Z01 NS 02275-05 LNNS	13	30	Z01 NS 02395-03 CDP	3	66
Z01 NS 02284-05 LNNS	13	72	Z01 NS 02396-03 CDP	3	68
Z01 NS 02286-05 LNNS	13	68	Z01 NS 02403-03 OBFS	1.A	73
Z01 NS 02293-05 LNP	15	21	Z01 NS 02404-03 OBFS	1.A	63
Z01 NS 02297-05 ODIR	7.B	39	Z01 NS 02405-03 OBFS	1.A	75
Z01 NS 02299-05 ODIR	7.B	41	Z01 NS 02406-03 OBFS	1.A	77

Intramural Research Projects - Numerical Listing (Cont'd)

PROJECT NUMBER	TAB	PAGE
Z01 NS 02407-03 OBFS	1.A	45
Z01 NS 02408-03 OBFS	1.A	43
Z01 NS 02409-03 OBFS	1.A	103
Z01 NS 02410-03 OBFS	1.A	107
Z01 NS 02411-03 OBFS	1.A	91
Z01 NS 02412-03 OBFS	1.A	99
Z01 NS 02413-03 OBFS	1.A	105
Z01 NS 02414-03 OBFS	1.A	95
Z01 NS 02415-03 OBFS	1.A	146
Z01 NS 02421-03 OBFS	1.A	97
Z01 NS 02423-02 ODIR	7.B	55
Z01 NS 02424-02 ODIR	7.B	57
Z01 NS 02425-02 LNNS	13	8
Z01 NS 02426-02 LNNS	13	9
Z01 NS 02428-02 LEN	24	2
Z01 NS 02429-02 LNC	17	42
Z01 NS 02430-02 LNC	17	45
Z01 NS 02431-02 CN	11	18
Z01 NS 02432-02 CN	11	20
Z01 NS 02433-02 DMN	12	51
Z01 NS 02434-02 DMN	12	55
Z01 NS 02435-02 DMN	12	59
Z01 NS 02440-02 CDP	3	70
Z01 NS 02441-02 CDP	3	73
Z01 NS 02442-02 OBFS	1.A	65
Z01 NS 02443-02 OBFS	1.A	41
Z01 NS 02444-02 OBFS	1.A	87
Z01 NS 02445-02 OBFS	1.A	89
Z01 NS 02446-02 OBFS	1.A	93
Z01 NS 02447-02 OBFS	1.A	101
Z01 NS 02448-02 OBFS	1.A	31
Z01 NS 02449-02 OBFS	1.A	32
Z01 NS 02450-02 OBFS	1.A	27

The following projects were initiated in Fiscal Year 1981:

PROJECT NUMBER	TAB	PAGE
Z01 NS 02451-01 ODIR	7.C	80
Z01 NS 02452-01 ODIR	7.C	88
Z01 NS 02453-01 DMN	12	63
Z01 NS 02454-01 SN	9	42
Z01 NS 02455-01 LNC	17	34
Z01 NS 02456-01 LNNS	13	10
Z01 NS 02457-01 LNNS	13	13
Z01 NS 02458-01 LNNS	13	16
Z01 NS 02459-01 LNNS	13	19
Z01 NS 02460-01 LNNS	13	22
Z01 NS 02461-01 LNNS	13	25
Z01 NS 02462-01 LNNS	13	46
Z01 NS 02463-01 LNNS	13	49
Z01 NS 02464-01 CDP	3	79
Z01 NS 02465-01 CDP	3	81
Z01 NS 02466-01 CDP	3	83
Z01 NS 02467-01 CDP	3	85
Z01 NS 02468-01 CDP	3	87
Z01 NS 02469-01 CDP	3	89
Z01 NS 02470-01 CDP	3	75
Z01 NS 02471-01 CDP	3	77
Z01 NS 02480-01 OBFS	1.A	111
Z01 NS 02481-01 OBFS	1.A	113
Z01 NS 02482-01 OBFS	1.A	115
Z01 NS 02483-01 OBFS	1.A	123
Z01 NS 02484-01 OBFS	1.A	125
Z01 NS 02485-01 OBFS	1.A	117
Z01 NS 02486-01 OBFS	1.A	129
Z01 NS 02487-01 OBFS	1.A	119
Z01 NS 02488-01 OBFS	1.A	127
Z01 NS 02489-01 OBFS	1.A	121
Z01 NS 02490-0 OBFS	1.A	131
Z01 NS 02491-01 OBFS	1.A	133
Z01 NS 02492-01 OBFS	1.A	135
Z01 NS 02493-01 OBFS	1.A	55
Z01 NS 02494-01 OBFS	1.A	83
Z01 NS 02495-01 OBFS	1.A	85
Z01 NS 02496-01 OBFS	1.A	59
Z01 NS 02497-01 OBFS	1.A	29
Z01 NS 02498-01 OBFS	1.A	47
Z01 NS 02499-01 OBFS	1.A	49
Z01 NS 02500-01 OBFS	1.A	51
Z01 NS 02501-01 OBFS	1.A	53
Z01 NS 02502-01 OBFS	1.A	57
Z01 NS 02503-01 OBFS	1.A	61
Z01 NS 02504-01 OBFS	1.A	37
Z01 NS 02505-01 OBFS	1.A	39
Z01 NS 02506-01 OBFS	1.A	31
Z01 NS 02511-01 EB	5.A	23
Z01 NS 02512-01 EB	5.A	25

TAB 1 -- OFFICE OF THE DIRECTOR -- OD/NINCDS (INCLUDES: EEO, OSHR, OPA)

ANNUAL REPORT

October 1, 1980 through September 30, 1981

Office of the Director, NINCDS

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

OFFICE OF THE DIRECTOR 1

EQUAL EMPLOYMENT OPPORTUNITY OFFICE (EEO) 3

OFFICE OF SCIENTIFIC AND HEALTH REPORTS (OSHR) 8

OFFICE OF PLANNING AND ANALYSIS (OPA) 16

OFFICE OF BIOMETRY AND FIELD STUDIES (OBFS) (See TAB 1.A)

Annual Report of the Acting Director
of the
National Institute of Neurological and
Communicative Disorders and Stroke
October 1, 1980 through September 30, 1981

Dr. Donald Tower, Director of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) retired from service as a Public Health Service Officer and Director of the Institute as of January 31, 1981. For the remainder of the fiscal year, the Institute's Deputy Director, Dr. Murray Goldstein, served as Institute Acting Director. Dr. Goldstein was assisted by Dr. Katherine Bick who served on assignment as Institute Acting Deputy Director; Dr. Bick is Deputy Director of the Institute's extramural Neurological Disorders Program.

The progress and success of the Institute's activities depend primarily on four essential elements: organization and administration; personnel; space; and fiscal resources.

Organization and administration: During the entire of fiscal year 1981, there have been no important changes in Institute organization. Previously approved plans are being implemented for the development of a research laboratory as a focal point for the Institute's intramural research activity on cerebral metabolism utilizing positron emission tomography (PET). Recruitment for the laboratory chief is being actively conducted; a PET scanner is in operation and the Institute is serving as the NIH administrative focal point for the development of a cyclotron facility. In addition, the Institute continues to pursue its objectives of establishing an intramural Clinical Communicative Disorders Branch in FY 1982 and of strengthening its intramural Epilepsy Section. Because of fiscal and personnel restraints, the Institute has begun an evaluation of the research endeavors of its intramural off-campus field stations, particularly Guam, and of the extramural anticonvulsant drug development program. The future scope of these activities will depend upon the results of these scientific and administrative reviews. Other organizational reviews and potential changes will await the appointment of the Director, NINCDS. Attention also will need to be given to intramural research activity in neuromuscular diseases and amyotrophic lateral sclerosis because of the retirement of Dr. K. Engel, the size and scope of the extramural Neurological Disorders Program, the future directions of the extramural Neural Prosthesis research activity, and the scope and direction of the research program of the Office of Biometry and Field Studies.

Personnel: Of all Institute resources, personnel is clearly the single most vital element influencing the productivity and effectiveness of the Institute's program. The skill and dedication of the scientific, administrative and support staffs of the Institute determine the success with which the Institute meets its responsibilities. Overall, the staff of the Institute continues to be highly productive, of reasonably high morale and dedicated to meeting the goals of the organization.

A key addition to the staff has been the recruitment of a new leadership team in the Office of Planning and Analysis (OPA) of the Office of the Director. The revitalization of this Office has already provided the Institute with an important staff service.

Several problems continue, however: The chief of these is the inability to recruit and retain key staff. The cap on salary ceilings makes NIH employment relatively non-competitive with the private sector. In addition, the present procedures of both the SES and Merit Pay systems make for frustration and exasperation on the parts of both supervisors and those being evaluated for potential "bonuses." These issues are causing considerable problems in the recruitment of top staff which are sorely needed to serve as key scientists and managers.

Despite the above, the successful accomplishment of the Institute's mission moves ahead with vigor because of the dedication of existing staff and its commitment to the objectives of the Institute's programs.

Space: Renovation of existing laboratory space in both research buildings and the clinical center continues to be a high priority issue. The presently available space is barely adequate and in some instances quite inadequate to meet the needs of the program. Hopefully, these renovations will begin in fiscal year 1982. In addition, little progress is being made in the development of an NIH extramural facility to replace the several off-campus locations housing the extramural program staff. The present extramural program space in the Federal Building is relatively adequate for program needs but isolates the NINCDS staff from continuing and necessary interaction with the extramural staffs of the other component parts of the NIH. Finally, it is anticipated that excellent additional research space will become available to the Institute with the opening of the ACRF in fiscal year 1982; the space has been allocated to the Institute investigators involved and negotiations are underway in regard to the installation of highly specialized equipment and facilities.

Fiscal resources: In times of overall national fiscal constraints, it is difficult to analyze and comment upon the fiscal resources available to the Institute. All in all, the fiscal needs of the NINCDS programs are receiving sympathetic consideration from all elements of the Department, the Administration and the Congress. It is an unfortunate coincidence that the scope and promise of the neurological and communicative sciences are literally exploding at the same time that the federal establishment must face serious fiscal constraints. The decade of the 1980's in research will clearly be the decade of the neurosciences as a broad base of fundamental information in cell biology, biochemistry, genetics and immunology can now be applied to the critical problems of nervous system function and disorders, including the problems of human communication. If ever there has been an opportunity to come to grips with knowing how the human brain works and how to prevent the catastrophic results of nervous system and communicative dysfunction, the 1980's hold that promise. Because of limited resources the Institute will have to make very difficult decisions among competing high priorities in order to invest resources in selected areas. Fiscal year 1981 was characterized by a fall of about 15 percent in the ability to pay approved grant applications as well as by a substantial decrease in the research contract program.

In summary and from an NINCDS leadership viewpoint, fiscal year 1981 was not characterized by any very important changes in the overall direction or implementation of the NINCDS program; the only exception to this was the retirement of the Institute Director. The Institute's research program activities intramurally and extramurally continue to be characterized by successful accomplishments despite constraints, but constraints similar to those affecting all of NIH. Because of the literal explosion of interest and research opportunity on problems of the nervous system and human communication, fiscal year 1982 promises to be one of continuing difficult choices among competing priorities.

ANNUAL REPORT
October 1, 1980 through September 30, 1981
Equal Opportunity Office
Office of the Director
National Institute of Neurological and
Communicative Disorders and Stroke

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) equal opportunity, affirmative action and civil rights activities are centered in the Equal Opportunity Office. This Office serves as principal advisory to the Director of the Institute and managers at all levels concerning positive application and vigorous enforcement of Affirmative Action and Civil Rights policies of the Federal government. It is responsible for coordinating and monitoring the enforcement of the 1964 Civil Rights Act and Executive Order 11246, in matters concerning the Institute's contracts and grants, coordinating the implementation of the Black College Initiatives (Executive Order 12232), and developing and implementing programs supportive of the Minority Biomedical Support (MBS) and Minority Access to Research Careers (MARC) Programs. The office also coordinates the NINCDS Community Outreach Programs to increase the representation of minorities and women in biomedical research, particularly the neurosciences.

The implementation of viable Affirmative Action and Civil Rights Programs that show results still continues to be a major program priority of the NINCDS. Although significant progress has been made in placing minorities and women in Administrative and Scientific positions, special initiatives and mechanisms are still needed to correct underrepresentation of minorities and women in the fields of biological and physical sciences, public information, the medical staff fellowship program, and key policy-making positions in the Institute. In FY'82, the Office will be developing a Five-Year Affirmative Action and Civil Rights Program to increase the representation of minorities and women at all levels of management and scientific research. The Plan will include future program directions and needs to increase the pool of Blacks, Hispanics, American Indians and women in the neurosciences.

PERSONNEL AND RESOURCES

On November 30, 1980, Mrs. Monretta Cooper was appointed to the position of Equal Employment Specialist. Mrs. Cooper will assist the Institute's Equal Employment Manager in the development and implementation of the Institute's Affirmative Action and Civil Rights Programs. Mr. Ricky Payne, a Technical Staff Assistant, was selected to direct the administrative and clerical activities of the office. The Institute also has an Equal Employment Opportunity (EEO) Advisory Committee which reports to the Director, an EEO Counselor that provides guidance and counseling to employees and applicants on the basis of discrimination, and a representative for the NIH Federal Women's Program.

SIGNIFICANT NINCDS AFFIRMATIVE ACTION ACCOMPLISHMENTS AND INITIATIVES IN FY'81

Recruitment and Placement

a. Two women (minority and non-minority) were appointed Administrative Assistant (341 job series) in the Intramural Research Program.

b. A Hispanic was appointed Personnel Officer for the Institute.

c. A woman was appointed Acting Deputy Director for the Institute.

d. Two minority Neurosurgeons were selected as Medical Staff Officers in the Surgical Neurology Branch.

Promotions

Thirty-five (35) employees received promotions during FY'81. Of this 35, seven (7) (or 16%) are minorities, and 28 (or 62%) are women. Six (6) received promotions at grade levels GS-9 and above. Of this 6, one (1) (or 8%) is a minority, and 5 (or 42%) are women.

Honors and Awards

The NINCDS Equal Opportunity Special Achievement Award was presented to Dr. Donald B. Tower, Director, NINCDS in recognition for "sustained" and "inspired" leadership in furthering the goals of equal opportunity and affirmative action during his tenure as Director of the NINCDS.

Dr. John W. Diggs, Deputy Director of the Institute's Extramural Activities Program was awarded the distinguished Ph.D. Alumni Award from Howard University for his role in research administration.

Under the Federal Incentive Awards Program, approximately 5 (or 10%) minorities and 19 (or 37%) women received awards (cash and quality increases) in FY'81.

MINORITY BIOMEDICAL SUPPORT (MBS) AND MINORITY ACCESS TO RESEARCH CAREERS (MARC) PROGRAMS

A postdoctoral fellowship in neuro-oncology, open to faculty members and students from minority institutions was announced by the Surgical Neurology Branch. Available under the NIH's MARC Program, the fellowship will provide an M.D. or Ph.D. with research experience in the area of human brain and spinal cord tumors.

The NINCDS will provide an additional $50,000 in FY'82 to support the MBS Program. The funds will be used for new starts and to cover commitments.

In the Institute's research laboratories, five (5) students were selected for summer positions, four (4) under the MBS Program, and one (1) under the MARC Program.

Arrangements have been made to receive two senior students on the MARC Honors Undergraduate Program from Central State University, Wilberforce, Ohio, to work in the Institute's research laboratories during the summer of 1983.

SUMMER PROGRAM

The participation of minority students in the NIH Summer Employment Program still is a major affirmative action initiative of the Institute. This Program provides on-the-job training and experience in biomedical research for students in high school, college, dental and medical school.

The Institute was given the authority to select 55 students for the 1981 Summer Program. Eight (8) (or 36%) were minority medical students, 14 (or 45%) were minority undergraduate students, and 11 (or 20%) were non-minority female students. These positions were located in the Institute's Intramural Research laboratories.

The NINCDS will continue to support the affirmative action efforts of the NIH Summer Employment Program, including the proposed Summer Research Fellowship Program for medical students. It is hoped that any revisions or cutbacks in the Program will in no way hamper the efforts to assure maximum participation of minorities, women and handicap students.

COMMUNITY OUTREACH ACTIVITIES

The NINCDS participated in the following conferences, workshops and symposiums in FY'81 to help promote the advancement of minorities and women in the neurosciences:

- The Minority Biomedical Symposium;
- The National Urban League;
- Blacks In Government (BIG);
- The National Medical Association Conference;
- Career Planning Job Fairs at Minority Schools;
- Workshop on Minorities in Health Careers at the University of Minnesota;

- North Carolina A&T State University Annual Symposium on Extramural Funding;
- National Conference of Hispanics and Native Americans in Science; and
- 12th Annual Federally Employed Women's (FEW) Conference

In conjunction with the Summer Externship Program at Provident Hospital in Baltimore, Maryland, medical students from Howard, Meharry, University of Maryland and Morehouse were selected for training assignments in the NINCDS clinical programs and laboratories.

The NINCDS provided funds to support a conference on "Puerto Ricans in Science."

Institute staff members participated in the Minority Faculty Development Conference at Harvard Medical School. The conference was designed to provide minority medical students in the New England area (Boston, Yale, Harvard and Tufts) with information concerning the development and opportunities in relationship to training, preparation and experience at NIH.

In cooperation with the Office of Scientific and Health Reports, and Mr. David Clarke from the University of Wisconsin, a full color recruitment brochure describing employment opportunities in the Institute was developed and distributed to minority scientists, conferences, workshops, schools and the general public.

NINCDS PUBLIC ADVISORY COMMITTEE

Dr. Sonya Sobrion, Assistant Professor of Pharmacology at Howard University was appointed to the Epilepsy Advisory Committee.

NIH VISITING PROGRAM

Dr. Adebaya Olumide, a Senior Neurosurgeon from the University of Ibadan, Nigeria, was appointed as a Visiting Scientist in the Surgical Neurology Branch, and Dr. Millicent Coker-Vann, a Microbiologist from Sierra Leone, was reappointed as a Visiting Associate in the Laboratory of Central Nervous System Studies.

FUTURE AFFIRMATIVE ACTION INITIATIVES

The NINCDS Five-Year Affirmative Action and Civil Rights Program will address the following areas to help correct underrepresentation of minorities and women in its workforce and the neurosciences.

- Recruitment and placement of minorities in the Medical staff Fellowship Program.

- Increasing the number of minorities in the Biology, Chemistry, Microbiology and Information Specialist job series.

- Ways to increase communication and awareness of NINCDS programs and activities to minority and women health professionals, communities and the general public.

- Increasing the representation of minorities and women in grades 9-12, 13-15 and 16-18, including the Commissioned Corps.

- Additional funds to support the Minority Biomedical Support Program.

- Increasing the representation of minorities and women in top level management positions.

- Researching alternative selection methods that will permit the Institute to hire MBS and MARC program graduates, and

- Ways to increase the participation of historically Black colleges and universities in NINCDS sponsored programs.

ANNUAL REPORT
October 1, 1980 through September 30, 1981

Office of Scientific and Health Reports
Office of the Director
National Institute of Neurological and Communicative Disorders and Stroke

Within the National Institute of Neurological and Communicative Disorders and Stroke, public information activities--including efforts to reach both scientific and lay audiences--are centered in the Office of Scientific and Health Reports (OSHR). This Office has the primary responsibility of advising the Institute Director and the Executive staff on ways to effectively report results of research conducted and supported by the Institute. Reporting tasks range from simply sending a pamphlet when someone asks for information, to writing and coordinating technical state-of-the-art reports on research in specific areas.

The OSHR consists of two sections: Public Inquiries and Publications. Both sections coped with staff shortages through much of this fiscal year. One writer/editor position in the Public Inquiries Section was vacant from November 1980 until May 1981 as OSHR grappled with hiring freezes and a shortage of qualified applicants. In the spring, however, the pool of applicants was suddenly enriched as other Department agencies cut their staffs. We hired a former employee of the National Institute on Drug Abuse, and she is now a full-time writer in the Public Inquiries Section. This year, too, the Section lost the services of Mr. Rufus Nedwards, a supply clerk with more than 30 years' employment at NIH. Mr. Nedwards was hospitalized for nearly five months before electing to retire in August. His position has been filled by Mrs. Maria Garavito, who joined OSHR last fall after being recruited through the EEO office. The Publications Section lost one writer early in the fiscal year, but a replacement was quickly found and brought on board just ahead of the hiring freeze. The end of the fiscal year, however, marks the end of a two-year agreement with the expert consultant responsible for revitalizing the Hope Through Research series of pamphlets. Four new HTR pamphlets were published and distributed during her stay, and five more are in various stages of production. Her loss will not be easily absorbed in FY 82. From time to time, the OSHR staff was augmented by the arrival of minority information interns. Cassandra Mims served with OSHR part-time throughout the fall of 1980, and Calvin Jackson was a full-time intern in the summer of 1981.

This year, OSHR oversaw information and publicity functions for the NINCDS-cosponsored First International Symposium on Tourette Syndrome in New York City, and for a consensus development conference on the Diagnosis and Treatment of Reye's Syndrome. Work is under way to provide similar support for a consensus development conference on computed tomographic scanning of the brain, set for November 4-6, 1981. OSHR involvement ranged from helping to develop graphic arts materials in support of the conferences, to advising as needed on ways to run a conference effectively, to editing proceedings. OSHR also continued its support of NINCDS workshops for voluntary health agencies concerned with neurological disorders.

The retirement of NINCDS Director Dr. Donald B. Tower on February 1 presented OSHR with an opportunity to place with the media stories reviewing his long career in the neurosciences. Tributes appeared in the NIH RECORD and many professional journals and voluntary agency newsletters. OSHR subsequently distributed announcements of the appointment of the Institute's Acting Director and Acting Deputy Director.

The Scientific Information Program Advisory Committee was disbanded in January 1981, since its original purpose--reviewing contracts for information activities--had been fulfilled. Committee members had also served as informal advisers to the OSHR. Since among the Committee's recently appointed members were experts in public relations, there are plans to retain these members' services on an ad hoc basis. Ways are also being sought of retaining lay members of the National Advisory Neurological and Communicative Disorders Council as advisers to OSHR once their term on the Council is completed. These plans may be hindered by severely restricted travel funds throughout the Institute.

The demand for publications and other information materials developed by OSHR remains high, especially when the NINCDS publication is the newest--and sometimes the only--information available on a topic. Three new publications proved to be extremely popular: "Alzheimer's Disease: A Guide for Health Practitioners," "Cerebral Palsy: Hope Through Research," and "The Dementias: Hope Through Research." The Guide won a first-placement prize in the 1980-1981 Blue Pencil Award competition sponsored by the National Association of Government Communicators. The cerebral palsy pamphlet won a third prize in this same competition.

The market for NINCDS publications apparently exceeds OSHR's ability to provide supplies. The Government Printing Office stocks and sells most of the Hope Through Research series and certain other NINCDS publications in which there is high public interest. However, the GPO price for a single copy can go as high as $2.50. Even with a discount for large orders, the costs have proven to be too high for voluntary agencies who need 20,000 copies or more. OSHR has worked with the voluntary agencies to develop alternate ways of publishing the pamphlets they want. Sometimes OSHR will loan camera-ready copy boards, enabling the agency to reprint their own supply of pamphlets. OSHR has also encouraged agencies to reprint the text and photographs from NINCDS pamphlets in their newsletters. With the continued moratorium on Federal publishing, it seems clear that these and other methods may become increasingly important in meeting the growing public demand for information about neurological and communicative disorders.

Public Inquiries Section

The Public Inquiries Section staff responds to correspondence and telephone inquiries about NINCDS research, programs and policies, coordinating replies as necessary with the Office of the Director, Intramural scientists and grantees, the NIH Director, and the DHHS Secretary.

By far the largest number of inquiries come from patients or families of patients with neurological and communicative disorders. The interest of these callers in research is highly personal, centering on the immediate application of research findings to the specific disease from which they or a family member suffer. However, health services--diagnosis, treatment, and rehabilitation--concern these callers even more than research. Information about new drugs and the Government's policy on drug development is requested regularly. Other frequently asked questions relate to financial help needed to meet heavy medical bills.

Responding to these questions not directly related to NINCDS research but touching on areas of research interest requires information specialists to acquaint themselves with the programs and policies of other components of the DHSS--Health Services Administration, Food and Drug Administration, and the Health Care Financing Administration, for example--and with state agencies through which services and financial aid are channeled. It is expected that with the planned decentralization of many health services, the staff will need to learn more about state health programs.

Last year 1,266 individually prepared responses were sent to the Institute's lay and medical audiences. Another 116 responses to controlled letters from the Congress and the White House were written and coordinated with the NIH Secretariat. Many other inquiries were answered with printed materials and notes of acknowledgement. In all, NINCDS responded to requests for 451,999 copies of publications, including 122,875 Hope Through Research pamphlets, 243,050 fact sheets, 3,658 monographs, 55,845 miscellaneous publications, 23,000 Special Reports, 3,658 monographs, and 3,573 National Research Strategy panel reports.

The dramatic increase in requests came about as the direct result of the promotion, by title, of specific publications in newspaper and magazine medical columns. This promotional effort, arranged by the NINCDS media liaison specialist, brought 6,000 requests for a pamphlet on Parkinson's disease; 9,000 requests for a pamphlet on headache; 10,000 requests for a pamphlet on hearing loss; and 15,000 requests for a pamphlet on stroke. The message is clear: the lay audience needs and wants information on neurological and communicative disorders. Next year, NINCDS will search for ways to satisfy this audience and, at the same time, comply with printing restrictions.

Public Inquiries Section personnel plan and develop the NINCDS annual exhibits program, and act as Institute spokespersons at the medical and scientific meetings to which the various exhibits are sent.

Last year the section contracted for the design of two new exhibits: an inexpensive modular unit that was sent to the meeting of the World Congress of Neurology in Kyoto and a flexible 10-panel unit that can be adapted by the scientific area for all of the major meetings the Institute attends.

The primary purpose of the exhibits program is to ensure an Institute presence at meetings of scientific societies whose interests identify closely with the mission of NINCDS. At these meetings NINCDS spokespersons alert members of the various societies--many of whom are Institute grantees or prospective grantees--to current research and research training programs, changes in award policies, and new scientific publications.

Last year the exhibit was shown at the following meetings of primary professional interest to the NINCDS: Childhood Neurology Society (Savannah); Society for Neuroscience (Cincinnati); American Speech and Hearing Associations (Detroit); American Association of Neurological Surgeons (Boston); American Academy of Neurology (Toronto); Triological Society (Vancouver); American Neurological Association (San Francisco); and the American Academy of Otolaryngology (New Orleans).

In 1979, the Institute undertook a pilot program to use its exhibit as a medium for informing health practitioners who work directly with patients about NINCDS research advances that are ready for clinical application. Last year, the Institute expanded this effort to include showing its exhibit not only at the American Academy of Pediatrics and the Association of Military Surgeons, both in Washington, D.C., but also at the annual meetings of the American Association of Medical Assistants in Kansas City, Missouri, and the American Nurses Association in Los Angeles. Information was also made available to neurological nurses--a group of special interest to the NINCDS--who visited the Institute booth at the American Association of Neurological Surgeons in Boston. Members of the above organizations were eager for information about diseases of the nervous system and showed special interest in NINCDS "Hope Through Research" pamphlets which they said helped them explain a disease or condition to their patients.

In cooperation with the NINCDS Equal Employment Opportunity Office, OSHR continued the Institute's effort to acquaint minority audiences with its research, research training, and patient information and education programs. The NINCDS EEO exhibit was shown last year at the Minority Biomedical Support meeting in Albuquerque and the National Medical Association in Atlanta.

Internal information activities received additional emphasis last year. The section informed NINCDS employees of intramural and extramural scientific achievements, personnel changes, and policy decision through more effective use of the bulletin boards in Building 31, and advised off-campus employees of these activities via the NINCDS Clips. The NINCDS Clips is a selective reprint of press clippings about Institute research, programs, and personalities which is distributed to laboratory and branch chiefs for posting within their work areas. The NINCDS Clips also was sent to voluntary health agencies and to NINCDS Council members.

The NIH Record is another forum that was used to reach NINCDS employees. Last year 21 news stories and 5 feature stories were prepared by writers in this section. A number of these stories were picked up by other publications for further dissemination.

The Public Inquiries Section provides materials for the Institute's Advisory Council meetings, updates the Council Directory, and plans the annual Council dinner. The head of the Section also serves as information liaison with the Extramural Activities Program and with the Program Directors in the Federal Building; she is responsible for identifying grantee research that is appropriate for use in Institute reports and publications, and writes annual special reports for congress on cerebral palsy and spinal cord injury.

Another series of pamphlets, produced annually by the Section, consists of special reports to Congress. These reports are summaries of the latest research in the various disorder areas; they are written by OSHR staff members in support of annual appropriations hearings, and then produced as booklets for distribution through the year. These reports are being used increasingly by voluntary agencies to keep their chapters posted on research developments. This year, five reports were published: Huntington's disease, multiple sclerosis, spinal cord injury, stroke, and hearing, speech, and language.

NINCDS's Office of Biometry and Field Studies operates a long-term program of hospital studies to produce authoritative statistics on incidence, prevalence, and costs of the major neurological and communicative disorders. A by-product of this program is a series of short, popular-format booklets presenting the distilled results of the studies. The first in this series, National Survey of Stroke, was produced and distributed by the Scientific Publication Section last year, and a second, National Head and Spinal Cord Injury Survey, was in press at the close of FY 81.

Two periodical issuances, not publications but essential to the OSHR's mission, are NINCDS Notes, a monthly Institute news service to journal editors, and Research Currents, a tri-annual packet of science news and other materials prepared for some 55 voluntary agencies sharing interests with NINCDS. Both issuances continued to be produced on schedule.

Various miscellaneous publications were produced during the year. An NINCDS Fact Book, reflecting the status of the Institute as of June 30, 1981, was readied for printing. Also prepared for printing was Epilepsy: A Manual for Health Workers, written originally for physicians and paramedical personnel in third world countries, but adapted by the Section for worldwide use. A full color brochure, The NINCDS Today, was being reworked by the Section. This project has fallen behind the production originally established in FY 80, and its speedy completion is being given high priority. An annual pamphlet, Voluntary Agencies Working to Combat Neurological and Communicative Disorders, was prepared and published. A revised guide, NINCDS Extramural Research and Training Awards, intended mainly for distribution at exhibits sent to professional society meetings, was produced.

The Section assisted several other Institute offices, including the EEOO with a brochure entitled Your Employment Opportunities at the NINCDS, and the Communicative Disorders Program with a pamphlet entitled Communicative Disorders Program: Guide to Programs and Awards.

A goal of the Section is to achieve a 4-part "family" of publications that will enable the Institute to tell its story to its various publics. The four publications will be the Fact Book, one annual issue of which has been published; the Institute brochure, The NINCDS Today, which is nearing completion and transmittal to the Government Printing Office; and guides on both the extramural and intramural programs. The extramural program guide produced in Fiscal 1981 will be updated and reprinted in a more attractive format, and the intramural guide is scheduled for production in Fiscal 1982.

Since 1975, the head of the Section also has served as the Institute's Freedom of Information Coordinator. In the interest of efficiency and cost effectiveness this function was transferred in August 1981 to the Grants Administration Section of the Extramural Activities Program. Prior to the transfer, the Section responded to 26 FOI inquiries about grants and 32 requests for summary minutes of Institute meetings.

Scientific Publications Section

The Scientific Publications Section produces and distributes publications for the general public and for a variety of scientific and professional audiences. The Section serves various administrative units of the Institute, *ad hoc* committees preparing reports, and outside organizations in the neurological and communicative disorders fields. The services include planning, clearance, writing, and editing of publications; securing and overseeing design, layout, and printing; distributing and storing publications; and subsequent revision and reprinting according to demand. The Section works with the NIH Printing Section, the Medical Arts and Photography Branch, and the Government Printing Office in producing publications, and also serves as the Institute's supply center for these materials.

The Institute's *Monograph Series* continues, with 24 titles published since 1960, 12 of which are still in print. A new monograph published in FY 81, *The NINCDS Collaborative Study of Brain Death*, was distributed to libraries, scientists, and others with an interest in the study.

A major project of the Publications Section has been revising, updating, and expanding the Institute's Hope Through Research pamphlet series. These pamphlets continue to be very popular with the general public. They provide information of interest and value to patients and their families, and describe research approaches to the various neurological and communicative disorders. During this fiscal year, new pamphlets on cerebral palsy, spinal cord injury, the dementias, and stuttering were published. At the close of the year, new pamphlets on epilepsy and shingles were in press, and new pamphlets on chronic pain, hearing loss, and brain tumors were in the final stages of production prior to printing. For the past two years, an expert consultant writer-editor has been devoting full time to the task of improving this series, and making the pamphlets more appealing to minority communities.

NINCDS fact sheets are another series of publications the Section has developed to meet a pressing need for information about lesser known neurological and communicative disorders. Eleven fact sheets are now in print, three new titles having been added in the past year: *Narcolepsy*, *Autism*, and *Autismo* our first Spanish-language fact sheet. Fact sheets on Friedreich's ataxia and on torsion dystonia are nearing completion.

A series of guides for professional health practitioners was begun in 1978 with *Diabetic Neuropathy--A Scientific Guide for Health Practitioners*. A second in this series, *Alzheimer's Disease--A Scientific Guide for Health Practitioners*, was published in FY 81 and widely distributed to nursing homes, voluntary agencies, and interested individuals. The Section plans to expand this series as time and resources permit.

In May 1981, a Departmental moratorium on printing was imposed so that a Department-wide survey of publications could be made. The moratorium did not seriously affect the Institute's FY 81 publications program because clearances had been obtained prior to the moratorium on on many of the publications that were being prepared, and were granted later on five others. Special case-by-case appeals for clearances may have to be prepared in FY 82, and future plans may have to be curtailed.

During 1981, a summer intern assigned to the Publications Section prepared 9 columns for "Search for Health," an NIH service to 500 weekly newspapers, two NIH Record items, and a brochure about the NIH summer intern program. Several members of the Section lent occasional assistance during the year to the NINCDS exhibits program, adapted Research Currents stories for the NIH Record, answered public inquiries, and undertook other writing and public information tasks not associated with publications.

Media Liaison

The Media Liaison effort, directed by the OSHR deputy chief, continues to respond to media inquiries and to kindle media interest in NINCDS research. This year, the OSHR undertook a modest community outreach project. The deputy chief accompanied the chief, OSHR, to Careers Day at a Washington high school with a predominantly minority population, to help answer students' questions about careers in public information. The deputy chief also joined an Epilepsy Branch scientist to discuss the Institute's brain research with a group of high school students in Maryland.

Local and national media coverage of NINCDS activities included a mix of print, television, and radio. A two-part series on spinal cord injury in the Journal of the American Medical Association highlighted NINCDS-funded regeneration research. The explosion of knowledge in the neurosciences was discussed on television by the Institute director at the time of his retirement. Useful information about the results of an NIH Consensus Development Conference on Reye's Syndrome was relayed swiftly to the American public as a result of advance work in stimulating press interest in the consensus panel's conclusions.

The attempted assassination of President Reagan and Press Secretary James Brady's head injury sparked a flurry of media inquiries about the brain throughout April. Since many NINCDS scientists were away at meeting at the time, many of the earliest questions were referred to the Secretary of the American Association of Neurological Surgeons. The AANS welcomed this move, and provided experts to help answer reporters' questions. NINCDS scientists, including the Institute's acting director, responded later to reporters writing followup stories or more comprehensive stories on brain research.

A superbly illustrated feature story on the brain in the October 1980 issue of GEO magazine described Institute-sponsored nervous system research. The article was admired by several television and print reporters, some of whom sought to imitate this fine example, and asked for OSHR's help in doing so.

In some instances, a ripple effect is produced, as for example when the GEO story was reprinted in The Reader's Digest. The Reader's Digest also reprinted from TIME magazine a story on back pain that quoted the Institute Acting Director.

Alzheimer's disease and spinal cord injury are attracting increasing media interest. ABC's "20/20" filmed an NINCDS Alzheimer's patient undergoing a PET scan and interviewed the Institute's Scientific Director for a segment on Alzheimer's disease to be aired this fall. CBS television plans an hour-long documentary on spinal cord injury and has sought the help of OSHR in arranging interviews with the Institute's Acting Director.

The power of the media is demonstrated by the response evoked when NINCDS publications are mentioned in national media. For example, as a result of Hugh Downs' interview with the Institute's Clinical Director on "Over Easy," nearly 7,000 requests for an OSHR pamphlet on Parkinson's disease were received. This interview has been re-broadcast several times since it was first filmed in late 1979.

OSHR strives to maintain its good relationship with media representatives, and to provide information rapidly to accommodate reporters' deadlines. This trust will be cultivated, and new ways sought to work in concert with OSHR's goals and Institute policy.

ANNUAL REPORT

October 1, 1980 through September 30, 1981

Office of Planning and Analysis

Office of the Chief

National Institute of Neurological and Communicative Disorders and Stroke

Fiscal year 1981 has been a year of change for this Office. In late 1980, its name was changed from the Office of Program Planning and Evaluation to the Office of Planning and Analysis. Dr. O. Malcolm Ray, its Chief during FY 1980, retired on December 31, 1980, and Mr. LeRoy Goldman succeeded him the following April. In addition, Mr. Joseph Culhane was recruited as Deputy Chief, OPA; Dr. Louis Steinberg was appointed Chief, Analysis and Reports Section (ARS); and Ms. Stephanie Hadley assumed the position of program analyst in ARS. Dr. Zekin A. Shakhashiri, who served as Acting Chief of OPA immediately following Dr. Ray's retirement, is now serving as Senior Medical Advisor to the Office.

OPA advises the Institute Director and OD staff as well as components of the intramural and extramural programs of the Institute on program development, analysis, evaluation, and the development of strategic and implementation plans. It provides staff support to facilitate the integration of the program planning, analysis, and evaluation efforts in the categorical program areas and provides the Director and the Executive Staff with assistance in coordinating the development of research plans for meeting these goals.

OPA develops, in collaboration with Program Managers and Directors, the Institute responses on a number of issues including analyses of specific aspects of research programs. It serves as the Institute representative at a number of trans-NIH and interagency coordinating committees, e.g., Arthritis, Digestive Diseases, Nutrition, etc. OPA also serves in a liaison capacity for reporting research on various subjects, e.g., prevention, toxicology, environmental health, technology transfer, etc., to other agencies, to NIH Institutes and offices, and as Clinical Trials Coordinator for NINCDS. In addition, OPA responds to a number of ad hoc queries from a variety of private and public sources regarding NINCDS research as it relates to NHLBI, NIEHS, pain research, research on the handicapped, etc.

Prevention analyses involved identification of the total NINCDS research matrix to extract FY '80 projects related to primary, secondary, and tertiary prevention. For fiscal year 1981, technology transfer activities required preparation of reports on NINCDS-related technology assessments, on technology Consensus Conferences -- Febrile Seizures, Reye's Syndrome, and CT Scan, including definitive listings and monitoring of NINCDS emerging technolgies for OMAR.

Analysis and Reports Section (ARS)

The Section prepares and coordinates the development of the Research and Legislative Plan of the Institute which is concerned with setting the major themes, thrusts, and tone for the discussion of budgetary requirements for future years. Input is also solicited and obtained from the Program Directors and from the Director and Deputy Director of NINCDS. Budgetary projections are developed by the Budget Office in close collaboration with the Section. Questions raised by NIH/OD are responded to jointly by the Budget Office and the Section.

ARS prepares and coordinates the annual Evaluation Plan for the research programs of the Institute and develops proposals for the recurrent assessment of the effectiveness of its research programs. The Institute has three approved evaluation projects which are funded by 1 percent set-aside evaluation funds. Two of these projects lie within the Communicative Disorders Program and one in the Intramural Research Program. Section staff also serves as Evaluation Contact and Institute representative in all activities related to evaluation. The Section provides NIH material requested by the Assistant Secretary for Planning and Evaluation regarding the status of ongoing evaluation projects and utilization of their findings and resulting impact. Specifically, e.g., ARS coordinated the development of program performance summaries on the Antiepileptic Drug Development Program and on the Speech and Language Disorders Program.

The Section coordinates the development of the annual Implementation Plan of the Institute. This involves setting funding priorities within the context of program objectives, research opportunities, and available resources. This is done in close collaboration with the NINCDS Office of the Director. In this process, the Section also develops the projections for new and renewal research grant applications to support the resource allocation decisions.

The Section also has the responsibility of coordinating development of the Institute Annual Report. The Section works with the Institute's Program Areas and provides them with technical assistance to assure uniformity of format and editorial quality of the Report. The Annual Report is a standard formal Institute document which presents an overview of the total scope of NINCDS research as to science, program, and budget.

As a legislative focus for the Institute, OPA has continued to work with appropriate staff of NIH/OD to monitor legislative developments in order to safeguard and maintain all elements of the Institute's mission. Legislative proposals pertaining to orphan drugs were reviewed and recommendations were forwarded to the Office of the Director.

Information Technology Section (ITS)

The Section is responsible for developing and maintaining administrative and program information systems for the Institute. The principal project under development is the Program Information System (PINS) which combines programmatic, fiscal, and management data into an integrated Institute-wide database. ITS was supported in this effort by two contractors: Pinkerton Computer Consultants for the development of computer programs and JRB Associates, Inc., to provide technical support to the Institute and to validate the programs developed by the programming contractor and ITS staff.

An integral part of PINS is an expanded classification system. The Section (1) developed the new multiaxis taxonomy with guidance from scientific staff of the Institute, (2) trained those scientists in the coding process, (3) performed data entry for all FY '81 applications and funded projects, and (4) coordinated the development of a coding form for FY '82 use.

Other significant activities of the Section include:

1. The design and development of an interactive system for the storage and retrieval of drug reaction data for inpatients as well as outpatients participating in clinical trials. Inpatient data is extracted from the Clinical Center's patient data file. Outpatient data, as well as any data corrections, can be entered into the system on-line from computer terminals. The system is in the final stage of development prior to release to the Intramural Program staff. Users have been trained and documentation is being developed.

2. Database administration for and maintenance of the Intramural Management Information System.

3. Development of label creation programs for the Office of Scientific and Health Reports, including user documentation and training.

ITS functions as the focal point in the Institute for both ADP Coordination and Security. The Section coordinates quarterly updating of the Institute's submissions to the Inventory of ADP Systems in the Public Health Service and to the NIH ADP Security Plan, and coordinates the Institute's submission to the annual ADP Plan. During fiscal year 1981, the Section developed an up-to-date inventory of Institute ADP resources including terminals, remote facilities, minicomputers, software systems/programs, and both ancillary and word processing equipment.

CONTRACT NARRATIVE
Office of Planning and Analysis, NINCDS
Fiscal Year 1981

NINCDS PROGRAM INFORMATION SYSTEM (PINS) (NO1-NS-82301), JRB Associates, Inc., 8400 Westpark Drive, McLean, Virginia 22101.

Title: Validation and Technical Support -- NINCDS Program Information System

Contractor's Project Director: Jacqueline Sanders

Allocation: $99,500

Objectives: The contractor is to: (1) provide technical support to the Institute by (a) developing all software related to data collection and conversion, (b) completing the interactive query and maintenance functions for high-priority PINS data categories, and (c) developing on-line and batch-scheduled reports for Accounts, Employees, and Positions data categories; (2) complete user and DBA documentation; (3) conduct user training as necessary focusing on interactive query, reporting, and update capabilities; (4) train the database administrator staff in ITS to use and maintain PINS; and (5) validate programs as they are developed by contractor staff or ITS staff.

Major Findings: For the first half of the year the contractor focused on validating programs completed by Pinkerton Computer Consultants. Subsequently, focus has been directed to data collection and conversion activities and providing technical support to the Institute: completing the interactive query and maintenance functions, reports development, participation in demonstrations of the system's capabilities, training users, and preparing user and DBA documentation.

Significance to the Program of the Institute: The scientific, budget, and program information of the Institute is increasing in quantity and complexity. Rapid access to pertinent facts in a timely manner is essential for effective management. PINS is being developed as a database management system providing on-line access to the data by organizational units throughout the Institute. Data will be accessible when and where they are needed and in a form that can be readily used. PINS will maintain data currency, validity, and compatibility between it and existing NIH systems such as IMPAC, CAS, ARMS,and CRISP.

Proposed Course: Following termination of the contract, the Information Technology Section, OPA, OD, NINCDS, will focus on completing the development and implementation of all remaining programs and will provide the full range of database administrator activities.

CONTRACT NARRATIVE

Office of Planning and Analysis, NINCDS

Fiscal Year 1981

NINCDS PROGRAM INFORMATION SYSTEM (PINS) (NO1-NS-9-2317), Pinkerton Computer Consultants, Inc., 65 West Street Road, Building C, Warminster, Pennsylvania 18974.

Title: Program Development and Implementation - NINCDS Program Information System

Contractor's Project Director: Dr. Dennis Clague

Allocation: $50,000

Objectives: The contractor is to write, test, install, parallel test, and document the computer programs for the NINCDS Program Information System (PINS). The contractor will insure the timely delivery of products which meet the specifications and requirements of the system. Four categories of data will be processed: Project Program Status and Reports (grants, contracts, and intramural projects), Operating Expenses, Budget/Program Analysis, and Personnel.

Major Findings: The system is being developed in modular fashion.

Significance to the Program of the Institute: The scientific, budget, and program information of the Institute is increasing in quantity and complexity. Rapid access to pertinent facts in a timely manner is essential for effective management. PINS is being developed as a database management system providing on-line access to the data by organizational units throughout the Institute. Data will be accessible when and where they are needed and in a form that can be readily used. PINS will maintain data currency, validity, and compatibility between it and existing NIH systems such as IMPAC, CAS, ARMS, TDCS, and CRISP.

Proposed Course: The contract terminated on February 25, 1981. The Information Technology Section, OPA, OD, NINCDS, assisted by JRB Associates, Inc., will complete development, implementation, documentation, and user training of the remaining PINS modules.

TAB 1.A -- OFFICE OF BIOMETRY & FIELD STUDIES -- OBFS/OD

ANNUAL REPORT
October 1, 1980 through September 30, 1981

Office of Biometry and Field Studies

Office of the Director
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

RESEARCH SUMMARY 1-5

Bibliography 6-8
IRP Consultants 9

CONTRACT NARRATIVES

Pilot Data Bank Network in Traumatic Coma 10
NO1 NS 9-2308
NO1 NS 9-2307
NO1 NS 9-2306

Pilot Data Bank Network in Stroke 12
NO1 NS 9-2302
NO1 NS 8-2397
NO1 NS 8-2396
NO1 NS 8-2398

Data Bank Maintenance Center for Pilot Data Bank Network Projects in Stroke and Traumatic Coma 13
NO1 NS 8-2390

Assessment of Data Bank Methodology 14
NO1 NS 0-2326

Nationwide Study of Stroke 15
NO1 NS 6-2333

Survey of Incidence, Prevalence and Costs of Head and Spinal Cord Injury 17
NO1 NS 4-2334

Case Verification and Supplemental HSCI Analyses 18
263-78-C-0132

Survey of Intracranial Neoplasms 19
NO1 NS 4-2336

Survey of the Incidence, Prevalence, and Costs of Multiple Sclerosis 20
NO1 NS 4-2335

Survey of Major Neurological Disorders in Copiah County, Mississippi 21
NO1 NS 7-2357

Table of Contents (cont'd)

Test of Study Design and Pilot Study for a National Survey of Epilepsy 23
N01 NS 8-2383

National Hospital Survey of Disease 24
(formerly Comprehensive Disease Statistics Survey)
Y01 NS 7-0030

ECA Dementia Supplement 26
1Y01 0-0004

PROJECT REPORTS

Spinal Manipulative Therapy as Treatment for Musculo-Skeletal Dysfunction in Athletes formerly titled "Study of Efficacy of Spinal Manipulative Therapy on the Performance of Athletes" 27
Z01 NS 02450-02 OBFS

INDO-U.S. Study of Head Injury 29
Z01 NS 02497-01 OBFS

Antibody Titers in Macacas on Cayo Santiago 31
Z01 NS 02506-01 OBFS

A Statistical Study of a Sensory-Decision-Theory Method in the Measurement of Experimental Pain 33
Z01 NS 02310-05 OBFS

Associations of Multiple Sclerosis with Certain Serological Parameters 35
Z01 NS 02342-04 OBFS

Estimation of the Incidence Rate of Disabling and Severe Headache 37
Z01 NS 02504-01 OBFS

Headache in Pregnant Women 39
Z01 NS 02505-01 OBFS

Development of Offline Data Entry System for Stroke and Coma Projects 41
Z01 NS 02443-02 OBFS

Clinical Databanks As a Resource for Epidemiologic Research 43
Z01 NS 02408-03 OBFS

Assessment of Databank Methodology 45
Z01 NS 02407-03 OBFS

CT Scan Observer Variability Study 47
Z01 NS 02498-01 OBFS

Table of Contents (cont'd)

Stroke Incidence in South Alabama 49
Z01 NS 02499-01 OBFS

Polymyositis/Dermatomyositis Study 51
Z01 NS 02500-01 OBFS

Myasthenia Gravis Study 53
Z01 NS 02501-01 OBFS

Stroke Diagnosis: The NINCDS Data Bank Algorithm 55
Z01 NS 02493-01 OBFS

Medical Studies Database System 57
Z01 NS 02502-01 OBFS

Preliminary Steps for a Data Bank Project in Epilepsy 59
Z01 NS 02496-01 OBFS

Cerebral Palsy Bibliography of Selected References 61
Z01 NS 02503-01 OBFS

National Survey of Chronic and Debilitating Headache 63
(Previously titled "National Headache Survey")
Z01 NS 02404-03 OBFS

Feasibility of a National Survey of Speech Defects 65
Z01 NS 02442-02 OBFS

Pilot Data Bank Network Project in Coma 67
Z01 NS 02340-04 OBFS

Pilot Data Bank Project Network in Stroke 69
Z01 NS 02238-05 OBFS

Type-Specific Stroke Mortality Trends 71
(Previously titled: "Stroke Mortality Study")
Z01 NS 02341-04 OBFS

The Incidence and Prevalence of Stroke 73
Z01 NS 02403-03 OBFS

Assessment of Strategies for Analyzing Data From Small Area 75
Health Surveys (Previously titled: "Assessment of Strategies
for Analyzing Data from Small Area Mortality Surveys")
Z01 NS 02405-03 OBFS

The Frequency of Neurological Disorders Among Hospital Discharges 77
Z01 NS 02406-03 OBFS

Development and Design of a Pilot Study for a National Survey of
Epilepsy 79
Z01 NS 02237-05 OBFS

Table of Contents (cont'd)

Design of Health Interview Survey Questionnaire Supplements (formerly "Design of Convulsive Disorder Questionnaires") 81
Z01 NS 02239-05 OBFS

The Prevalence of Multiple Sclerosis in Colorado 83
Z01 NS 02494-01 OBFS

Analysis of Data From the National Survey of Multiple Sclerosis 85
Z01 NS 02495-01 OBFS

Statistical Coordinating Center for the Phenobarbital Clinical Study (previously titled "Cognitive and Behavioral Effects of Phenobarbital in Young Children"). 87
Z01 NS 02444-02 OBFS

A Phase II Clinical Trial of Lisuride versus Bromocriptine (previously titled "A Clinical Trial of Bromocriptine and Lisuride for the Treatment of Parkinson Disease"). 89
Z01 NS 02445-02 OBFS

Survey of Practice in the Management of Febrile Seizures (previously titled "Survey of Management of Children with Febrile Seizures"). 91
Z01 NS 02411-03 OBFS

Parkinson's Disease in Twins (previously titled "Parkinson Twin Studies"). 93
Z01 NS 02446-02 OBFS

Early Stopping Rules Used in Clinical Trials (previously titled "Simulation of Early Stopping Rules Used in Clinical Trials"). 95
Z01 NS 02414-03 OBFS

Assessment of Robustness of Missing Data Techniques 97
Z01 NS 02421-03 OBFS

Consensus Meeting on the Management of Children with Febrile Seizures 99
Z01 NS 02412-03 OBFS

A Prospective Study of Low Birthweight Infants 101
Z01 NS 02447-02 OBFS

Image Reconstruction Theory 103
Z01 NS 02409-03 OBFS

Study of Lisuride for the Treatment of Parkinson Patients 105
Z01 NS 02413-03 OBFS

Dual Energy Scanning 107
Z01 NS 02410-03 OBFS

Table of Contents (cont'd)

Maternal Infection Study (Previously titled "Methodology for Systematic Analysis of Multiple Antibody Readings on Matched Controlled Studies"). 109
Z01 NS 02312-05 OBFS

A Clinical Study of Bromocriptine and Pergolide for the Treatment of Parkinson's Disease 111
Z01 NS 02480-01 OBFS

The Use of Phantom Views to Diminish an Artifact in CT Scans 113
Z01 NS 02481-01 OBFS

Optimization of Software for PET Scanner 115
Z01 NS 02482-01 OBFS

Response of Cultured Postimplantation Mouse Embryos to Potential Teratogenic Effect of Phenytoin and Valproic Acid 117
Z01 NS 02485-01 OBFS

Nonparametric Confidence Limits for Survival Probabilities and Quantiles 119
Z01 NS 02487-01 OBFS

Evaluation of the Effectiveness of Information Services Provided to Specialists in Communicative Disorders by MEDLINE 121
Z01 NS 02489-01 OBFS

Predictive Value of the EEG in Febrile Seizures 123
Z01 NS 02483-01 OBFS

Statistical Coordinating Center for Communicative Disorders Program Projects 125
Z01 NS 02484-01 OBFS

Interactive Computer System for Patient Entry and Randomization for Clinical Study 127
Z01 NS 02488-01 OBFS

Statistical Models of In Vitro Mutagenicity Assays 129
Z01 NS 02486-01 OBFS

Research in Statistics 131
Z01 NS 02490-01 OBFS

Activities of Daily Living Following Stroke 133
Z01 NS 02491-01 OBFS

Data Support for Diagnostic Algorithms of Stroke 135
Z01 NS 02492-01 OBFS

Etiology and Natural History of Convulsive Disorders and Cerebral Palsy 137
Z01 NS 02114-08 OBFS

Table of Contents (cont'd)

Clinical Trial of Efficacy of Phenobarbital as Prophylaxis for Children with Febrile Seizures 140
Z01 NS 02354-04 OBFS

Epidemiology of Disabling Headache 142
Z01 NS 02449-02 OBFS

Supraorbital Opacity Pulses During Carotid Artery Compression: A Method for the Detection of Carotid Obstruction 144
Z01 NS 02448-02 OBFS

Cage Standards for Primates 146
Z01 NS 02415-03 OBFS

Annual Report
for period October 1, 1980 through September 30, 1981
Office of Biometry and Field Studies
Office of the Director
National Institute of Neurological and Communicative Disorders and Stroke

The Office of Biometry and Field Studies (OBFS) supports a program in biostatistics and computer science to further medical research in the areas of neurology and communicative disorders.

OBFS is active in a number of program areas, such as disease-specific computerized clinical data banks and national surveys of disease, and there has also been a considerable increase in the Branch's clinical trial activities, both intramurally and in consultation with university-affiliated groups that do clinical research.

In addition, Intramural Program research collaboration continues to be an important element of OBFS activities, and OBFS investigators participate fully in all phases of the projects in which they are involved. The range and variety of problems utilize the varied talents of the OBFS staff which, in addition to mathematical statistics, include those of physics and computer science. The latter two, for example, are extensively relied upon for the work in computer-aided tomography.

In the area of clinical trials, OBFS has collaborated with the Experimental Therapeutics Branch (IP) on clinical studies of Parkinson's disease. Both in-patient and out-patient clinical trials of new drugs or the new application of standard drugs (e.g., lisuride, bromocriptine, lithium) have been initiated with Parkinson's disease patients. OBFS has been involved in the design and analysis of these trials as well as in the monitoring of the accumulating data and the analysis of adverse reactions.

OBFS is the statistical coordinating center for several continuing or planned clinical trials. It is developing the statistical coordinating center for a clinical trial, with the Developmental Neurology Branch (NDP), that addresses the issue of the potential loss of cognitive function in children who have febrile seizures and are being treated with phenobarbital.

In collaboration with the Communicative Disorders Program, OBFS is planning a trial on the evaluation of communicative and social skills acquired by the congenitally deaf through language learning.

OBFS is participating in the design of a clinical trial on the efficacy of spinal manipulative therapy as a treatment for musculo-skeletal dysfunction on the performance of athletes, in collaboration with the Office of the Director, NINCDS, and Yale University.

OBFS has been actively consulting on a number of clinical trials. These include the clinical trial of persistent otitis media with effusion with Dr. Gates at the University of Texas at San Antonio; the cooperative study of plasmapheresis in acute Guillain-Barré syndrome with Dr. McKhann of the Johns Hopkins University; the study of Copolymer I in multiple sclerosis with

Dr. Bornstein at Albert Einstein College; the study of plasmapheresis in multiple sclerosis with Dr. Weiner at the Children's Hospital Medical Center in Boston; the clinical trial of multiple sclerosis using calcium, magnesium and Vitamin D, with Dr. Scheinberg at Albert Einstein College; and the trial of amantadine in multiple sclerosis, with Dr. Ellison at UCLA. OBFS also provides a member of the monitoring committees for the extracranial/intracranial bypass study and the Copolymer I clinical trial.

OBFS is responsible for the NINCDS Stroke and Traumatic Coma Data Bank Projects as well as for providing computer and systems support to the Extramural Programs of NINCDS.

Near completion are interactive computer and data management systems which will be used to support clinical trials. These systems will utilize the DCRT computer and the Hewlett-Packard minicomputer of OBFS for registering patients entering clinical trials, checking their eligibility, and randomly allocating eligible patients to treatments. These systems will also expedite data entry and management, ascertainment of patient status, data tracking, data quality assurance, and the production of simple charts and tables.

The Stroke Data Bank has met the objectives of its pilot phase and is entering its main phase. Meanwhile, studies from data of the pilot phase include the testing of a new diagnostic algorithm for stroke and its relationship to laboratory evidence; activities of daily living as a prognostic index, characteristics of lacunar strokes; etc. Manuscripts are being prepared for publication on these research studies as well as on the background and objectives of the project. At the June 1981 meeting of the Society for Epidemiological Research, the results of the stroke incidence study (a component of the south Alabama population-based Stroke Data Bank) were presented.

The pilot Traumatic Coma Data Bank is composed of six clinical centers in the United States, and has collected data on over 300 comatose, head-injured patients since June 1981. Studies are under way to relate accident details, injury characteristics and complications to outcome (both short-term, and at 3, 6, 12 and 24 months post-injury). In addition, several studies on the quality of these data include, for example, an experiment on inter-observer agreement in CT Scan reading. A manuscript on the objectives and methods of the Coma Data Bank is being prepared for publication.

The development of a vocabulary and a series of hypotheses for an Epilepsy Data Bank is progressing. Serious consideration is being given to the potential use of a data bank to test the new international classification system for epilepsy. Regular consultation with epilepsy experts is planned to determine the feasibility of implementing such a data bank and to determine the appropriate role of OBFS in this endeavor. At the request of university-affiliated investigators, OBFS is participating in a consultant role to aid in developing drafts of data collection forms for their planned data banks on myositis and myasthenia gravis.

An ad hoc meeting of headache experts and directors of headache clinics was held in the Spring of 1981 to discuss plans for the National Survey of Chronic and Debilitating Headache. With the support and participation of this group data collection began for a feasibility study. Headache patients from several major headache clinics are being interviewed by telephone to validate a specially designed questionnaire, and their clinical records will be reviewed as part of the development of a classification system.

Since a major survey is time consuming and requires considerable oversight, its justification must depend on the pursuit of highly focused scientific objectives, as well as the more typical, and broader, demographic and epidemiologic goals. Specific hypotheses can be generated for which the survey can provide useful information. Some of the areas for hypotheses development include menstruation, pregnancy, use of oral contraceptives, hypertension and a variety of diseases. Other objectives of the Headache Survey will be: (1) to identify clinical, psychological, and environmental risk factors which may be associated with the occurrence of several major types of headache; (2) the testing of a different classification system for types of headache which can be used in epidemiologic studies, using the symptomatology and history reported by patients; (3) to measure the prevalence of headache disorders in the United States, to describe the major types of headache by demographic characteristics and to identify high risk groups; and (4) to determine the impact of headaches on society by demographic subgroups of the U.S. population; factors such as financial cost, work, productivity loss, and quality of life will be assessed, as well as patterns of medical care.

A pilot study which tested the methodology for a proposed national survey of epilepsy has been completed and a report will be made to the OBFS Advisory Committee at its November meeting. The report will contain an assessment of the adequacy of the methodology for use in a large-scale survey. Support for a national study will be considered by the Advisory Committee.

The National Hospital Survey of Disease, a joint effort with the National Center for Health Statistics (NCHS), has completed its feasibility study at 27 hospitals. The National Survey will "piggyback" on the NCHS Hospital Discharge Survey. The data are being analyzed. The objective of this project is to determine whether the NCHS, using a modification of an existing annual NCHS survey, can periodically obtain hospital incidence and prevalence data for a number of neurological and other disorders, in order that trends in the relative frequency of these disorders can be identified. The long-term objective of this project is to provide NIH medical expertise to NCHS and recognition and support for NCHS to provide these data to NIH on a routine basis.

Analysis of data and preparation of reports continue for the Copiah County Study, a survey of a community in rural Mississippi. This study is the first to provide comparisons of the prevalence of major neurological disorders (cerebral palsy, psychomotor delay, epilepsy, stroke, Parkinson's disease, and dementia) between blacks and whites in a rural setting. An epilepsy questionnaire was also tested in the Mississippi Study for possible use in NCHS's Health Interview Survey.

The senile dementia study is in progress, in cooperation with the National Institute of Mental Health and the Johns Hopkins University. The study is based on medically validated cases and will generate estimates of the social and economic costs of the disease on the affected individuals and their families.

OBFS is expanding its study activities in multiple sclerosis. In collaboration with Dr. Scheinberg and his associates at the Albert Einstein

College of Medicine, OBFS is analyzing the psychosocial data of the National Survey of Multiple Sclerosis. The Rocky Mountain Multiple Sclerosis Center believes that the prevalence of multiple sclerosis in Denver is much higher than anticipated, so a small collaborative study is being considered to determine whether the study of the incidence and prevalence of multiple sclerosis in Colorado, or in the Denver region, is feasible, and whether it can be accomplished inexpensively.

A significant effort continues to be focused on the analysis of data from the Collaborative Perinatal Project. Intensive studies are proceeding in the areas of febrile seizures, neonatal seizures, convulsive disorders, cerebral palsy, and maternal infection during pregnancy.

Implementation of a multi-stage program is progressing to determine the optimal management of children with febrile seizures. The consensus meeting held in the previous fiscal year delineated several areas of needed research including (1) the usefulness of the EEG in predicting later recurrence of seizures in children with a febrile seizure and (2) the possible harmful side effects on cognitive function of administration of chronic phenobarbital to children with febrile seizures. In collaboration with the Developmental Neurology Branch, OBFS has initiated two major research studies to answer these questions. OBFS is also implementing a survey of current practice and of clinical determinants and rationale for management of children with febrile seizures.

The Departments of Neurosurgery at the University of Virginia and the All-India Institute of Medical Sciences at New Delhi, India, and OBFS are planning a joint Indo-U.S. Study of Head Injury. While important objectives of the proposed study relate to the comparisons of the populations at risk in New Delhi and in the Charlottesville, Virginia area, the major interest is to examine iatrogenic complications of head injury, such as infection. OBFS will serve as the center for data analysis and data coordination.

OBFS is involved in the planning of a clinical investigation of the prognostic values of CT scanning in low birthweight children, in collaboration with the Developmental Neurology Branch and Children's Hospital of D.C. Data coordination and analysis will be performed by OBFS.

OBFS continues to collaborate actively with scientists in the Intramural Research Program, working on a wide range of subjects, including methods for enhancement of computer-aided tomography, assessment of regimens for Parkinson's disease and assessment of the potential teratogenic effect of phenytoin and valproic acid.

OBFS scientists are also conducting research into the development and improvement of statistical methodology to meet the needs of NINCDS in design of experiments, analysis of data, and statistical modeling of biological processes and phenomena. Current studies include methods of non-parametric regression, determination of sample sizes for clinical trials with multinomial outcomes, regression in Poisson data, sequential methods with early stopping, two-period cross-over designs for Phase II clinical trials, regression methods for survival data, and Markov modeling of clinical features of Parkinson's disease.

Members of the Neurological Disorders Program and OBFS have completed the book Minimal Brain Dysfunction: A Prospective Study, published in the Spring of 1981 by Lawrence Earlbaum Associates. Other collaborators in the Developmental Neurology Program and OBFS are at work on two books -- one on the relationship of maternal variables and childhood signs to cerebral palsy, the other on the association of these variables to seizures in children.

Findings from the national surveys of neurologic disease continue to be disseminated. A monograph, The National Survey of Stroke, has been published as a supplement to Stroke: The Journal of Cerebral Circulation. This monograph presents the findings of the survey, and provides statistics on the clinical aspects, epidemiologic factors, and economic impact of stroke. A brochure for a lay audience on the findings of the Stroke Survey has also been distributed.

A comprehensive report on the Head and Spinal Cord Injury Survey has been published as a supplement to the Journal of Neurosurgery. This report includes a review of the relevant literature on injury to the head and spinal cord, a discussion of the design and methodology of the survey, a presentation of the major findings, an assessment of some uncertainties that affect the findings, and a comparison of findings from the survey with those of other surveys.

A report on the findings from the Survey of Intracranial Neoplasms has been prepared for submission to the Journal of Neurosurgery.

A brochure on the Head and Spinal Cord Injury Survey is in press.

The book Febrile Seizures, derived from the Consensus Conference, will be published in the early Fall by Raven Press.

The Survey of Multiple Sclerosis has been completed. A report on the incidence and prevalence of the disease, the first of a series of articles, has been accepted for publication in the Annals of Neurology.

A special session on the NINCDS National Surveys of neurologic disorders was held at the October 1980 meeting of the American Public Health Association. Presentations were made on the methodology and findings of three surveys -- stroke, intracranial neoplasms, and head and spinal cord injuries. These surveys, based on national probability samples of hospital records, were designed to furnish estimates of the incidence, prevalence, and economic costs of these disorders.

OBFS maintains and fosters an active interest within NIH and elsewhere in methodological issues in the application of statistics to medicine. The Branch sponsors a bimonthly journal club for NIH statisticians in which controversial topics are discussed and debated. The Branch also occasionally sponsors sessions at professional meetings such as those of the Biometric Society on topics of methodological interest to OBFS and the Institute. This year OBFS organized an invited session on early stopping rules in clinical trials.

OFFICE OF BIOMETRY & FIELD STUDIES
Bibliography

Anderson, D.W. and McLaurin, R.L. (Eds.) "Report on the National Head and Spinal Cord Injury Survey." Supplement to the Journal of Neurosurgery, November, 1980.

Anderson, D.W., Kalsbeek, W.D., and Hartwell, T.D. "The National Head and Spinal Cord Injury Survey: Design and Methodology." Journal of Neurosurgery 53: S11-S18, 1980.

Anderson, D.W. and Kalsbeek, W.D. "The National Head and Spinal Cord Injury Survey: Assessment of Some Uncertainties Affecting the Findings." Journal of Neurosurgery 53: S32-S34, 1980.

Baum, H.M. and Goldstein, M. "Cerebrovascular Disease Type Specific Mortality: 1968-1977". Presented at the First Annual Symposium on Brain-Heart Relationships, Jerusalem, 1980.

Baum, H.M. "An Examination of the Demographics of Stroke Victims Using Prevalence and Mortality Data." Public Health: Journal for the Society of Community Medicine 95: 9-14, 1981.

Baum, H.M. and Robins, M. "Chapter 5: Survival and Prevalence." In Weinfeld, F.D. (Ed.) The National Survey of Stroke. Stroke 12 (Part II): I-59 - I-68, 1981.

Baum, H.M. and Rothschild, B. "The Incidence and Prevalence of Reported Multiple Sclerosis." Accepted for publication by Annals of Neurology.

Baum, H.M. and Weinfeld, F.D. "Summary Findings from the National Multiple Sclerosis Survey-U.S.A." Presented at the 12th World Congress of Neurology, Kyoto, 1981.

Gross, C.R. and Dambrosia, J.M.: Quality Assurance for Clinical Data Banks. Proceedings of the Fifth Annual Symposim of Computer Applications. (In press)

Gross, C.R., Kase, C.S., Shear, C.L., and Moher, J.P. "Stroke Incidence in South Alabama". Presented to the Society for Epidemiological Research meeting, June, 1981, to be submitted for publication.

Eisler, T., Dambrosia, J., et al. Letter to the Editor. Neurology, (In press)

Ellenberg, J.H. Book review of Clinical Trials, by Schwartz, Flamant and Lellouch, Biometrics, 1981.

Ellenberg, J.H. and Nelson, K.B. Long-term Clinical Trial on Use of Prophylaxis for Prevention of Recurrences of Febrile Seizures and Epilepsy. Presented at the Consensus Meeting on the Long-term Management of Children with Febrile Seizures, National Institutes of Health, May 1980. To be published in Febrile Seizures, Raven Press, 1981.

Ellenberg, J.H. and Nelson, K.B. "Predictions of Cerebral Palsy at Four Months of Age." Developmental Medicine and Child Neurology, 1981, (with Editorial Comment).

Ellenberg, J.H. and Nelson, K.B. "Published Recommendations for the Treatment of Febrile Seizures: Their Efficiency vs. Epilepsy." presented at the Consensus Meeting on the Long-term Management of Children with Febrile Seizures, National Institutes of Health, May 1980. To be published in Febrile Seizures, Raven Press, 1981.

Goldstein, M. and Chen, T.C.: Epidemiology of Disabling Headache. Proceedings of the International Headache Congress. Florence, Italy. 1981.

Gopinathan, G., Ward, C., Dambrosia, J., et al. Lisuride in Parkinson Disease. Neurology, Vol. 31, No. 4, April 1981.

Kunitz, S.C., Gross, C., Nichols, B.J., Edelstein, S.L.: "A National Traumatic Coma Data Bank". Proceedings for Fourth Annual Symposium on Computer Applications in Medical Care. Nov. 2-5, 1980: P. 1333, 1339.

Lee, Y.J. Test of Trend in Count Data: Multinomial Distribution Case. Journal of American Statistical Association, Volume 75, December 1980, pp. 1010-1014.

Lee, Y.J. Nonparametric Selections in Blocked Data: Application to Motor Vehicle Fatality Rate Data. Technometrics, Vol. 22, November 1980, pp. 535-542.

Lee, Y.J. and Wesley, R.A. Statistical Contributions to Phase II Trials in Cancer: Interpretation, Analysis and Design. Seminars in Oncology, in press.

LeWitt, P., Ward, C., Dambrosia, J., et al. Lisuride Versus Bromocriptine Treatment in Parkinson Disease: A Double Blind Study. Neurology, in press.

Nelson, K.B. and Ellenberg, J.H. "Apgar Scores as Predictors of Chronic Neurologic Disability." Pediatrics, July 1981.

Nelson, K.B. and Ellenberg, J.H. "Febrile Seizures," Childhood Epilepsy, PSC Publishers, Littleton, Massachusetts, 1981.

Nelson, K.B. and Ellenberg, J.H. "The Role of Recurrences in Determining the Outcome in Children with Febrile Seizures." Presented at the Consensus Meeting on the Long-term Management of Children with Febrile Seizures, National Institutes of Health, May 1980. To be published in Febrile Seizures, Raven Press, 1981.

Nelson, K.B. and Ellenberg, J.H. editors, Febrile Seizures, Raven Press, 1981.

Nichols, P.L. and Chen, T.C.: Minimal Brain Dysfunction: A Prospective Study. Lawrence Erlbaum Associates, Publishers, Hillsdale, New Jersey. 1981.

Nichols, B.J., Rush, R.L., Moss, P., Edelstein, S.L., Fishman, I., Kunitz, S.C.: Data Entry for Multiple Centers - A Microprocessor Approach. Proceedings of the Computer Applications in Medical Care, in press.

Robins, M. and Baum, H.M. "Chapter 4: Incidence." In Weinfeld, F.D. (Ed.) The National Survey of Stroke. Stroke 12 (Part II): I-45 - I-68;, 1981.

Simon, R. and Lee, Y.J. Nonparametric confidence limits for survival probabilities and the median. Cancer Treatment Reports, in press.

Travaninen, H., Calne, C., Dambrosia, J., et al. CSF Hydroxlase Cofactor in Normal Ageing. Neurology, Neurosurgery, and Psychiatry, in press.

Ward, C., Sanes, J., Dambrosia, J., and Calne, D. Methods for evaluating treatment in Parkinson Disease. To appear in Advances in Neurology, D. Calne, ed., in press.

Weinfeld, F.D. (Ed.) The National Survey of Stroke, Stroke 12, Suppl. 1 (Part II): Charlottesville, VA, American Heart Association, Inc., 1981, I 91 pp.

Weiss, W. and Weinfeld, F.D.: Introduction. In Weinfeld, F.D. (Ed.): The National Survey of Stroke, Stroke 12, Suppl. 1 (Part II), Charlottesville, VA, American Heart Association, Inc., 1981, pp. I 3-I 5.

Weiss, W. (Author): National Survey of Stroke. Conducted by Westat Research, Rockville, Maryland under Contract No. 1-NS6-2333, Office of Biometry and Field Studies, National Institute of Neurological and Communicative Disorders and Stroke, U.S. Department of Health, Education, and Welfare, Public Health Service, NIH Publication No. 80-2069, 1980, pp 14.

OFFICE OF BIOMETRY & FIELD STUDIES
Section on Mathematical Statistics

Consultation with IRP

Dr. Yaar, Neuromuscular Section, Medical Neurology Branch: The effect of L-Dopa on EMG (electromyogram) measurements in human subjects.

Dr. Isabel Shekarchi, Infectious Diseases Branch: Determination of Rubella Antibody Levels using ELISA.

Dr. T. Chase and Ms. Sue Pollard, Intramural Research Program: Parkinson Patients on Guam.

Drs. Calne and Teravainen, Experimental Therapeutics Branch: LISURIDE Treatment of Parkinson Patients and Tetrahydrobiopterine Levels in aging.

Dr. Paul Fedio, Clinical Neuroscience Branch: BH4-levels and Pschometric Function.

Dr. John Barringer, Developmental and Metabolic Neurology Branch: Sample Size Determination for Detecting Differences Between Biopsy Methods for GLI and PE.

Dr. David Asher, Laboratory of Central Nervous Systems Studies: Comparability of Cell Cultures: A case-control study of copped cell for scrapie.

Dr. Christopher Ward, Experimental Therapeutics Branch: Study of Parkinson's Disease in Twins and study of Objective measurements of Movement Disorders.

Dr. Rodney Brooks, Neuroradiology and Computed Tomography Section: Surgical Neurology Branch, Enhancement of CAT and PET scanning techniques and optimization of PET Scanner Software.

Dr. John L. Sever, Infectious Disease Branch: Study of Toxoplasmosis in pregnant women, Study of relation of serological infection during pregnancy to outcome in children.

Dr. Roswell Eldridge, Section on Epidemiology: Parkinson Twin Studies.

Dr. George H. Weiss, Physical Sciences Laboratory, DCRT, the Use of Phantom Views to Diminish an Artifact in CT Scans.

Dr. David Lust, Laboratory of Neurochemistry, NINCDS: Gluscose and glycogen concentrations in cerebellum and cerebral cortex regions of the mouse nervous system.

Dr. William B. Marks, Intramural Research Program, NINCDS: Statistical analysis methods in neuronal spike data.

Dr. William T. London, Infectious Disease Branch, IR, Estimation of Sample Sizes for Testing Positive Antibody Titers in Macacas on Cayo Santiago.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1981

1.	Univ. of Texas-Galveston and Baylor Univ. Medical College	(N01-NS-9-2308)
2.	Univ. of Cal. in San Diego	(N01-NS-9-2309)
3.	Medical College of Virginia	(N01-NS-9-2307)
4.	Univ. of Virginia	(N01-NS-9-2306)

Title: Pilot Data Bank Network in Traumatic Coma

Contractors' Principal Investigators

1. Dr. Howard Eisenberg
2. Dr. Lawrence Marshall
3. Dr. Donald Becker
4. Dr. John Jane
5. Dr. Robert Grossman
6. Dr. Kamran Tabaddor

Current Annual Level FY'81

1.	$150,000
2.	126,000
3.	128,000
4.	101,000

Objectives: The primary objective of this project is to develop a computerized interactive data bank network for traumatic coma patients. This data bank will be used for clinical research and patient management.

Major Findings: This data bank project has developed and is utilizing a uniform vocabulary to collect patient data which will include the details of the accidents in test results, therapies and outcomes. The Glasgow Coma Scale is part of this vocabulary. Over 350 severely head injured patients were accrued as of June 1981 and data collection is continuing.

Significance to the NINCDS Program and Biomedical Research: The Traumatic Coma Data Bank Project is important for several reasons. Longitudinal data on severely head injured traumatic coma victims are collected at six centers using uniform definition and procedures. This information will provide a large body of high quality data for clinical research on the factors influencing survival and quality of life following severe head injury. In addition, the data bank will serve as an efficient mechanism for collecting, storing and retrieving the information collected on a single patient and groups of patients. The number of therapies and monitoring devices commonly utilized during the acute phase of managing traumatic coma necessitates a highly organized data handling capacity.

Proposed Course of the Project: This is a three-year collaborative pilot project involving six centers which collect patient data, a Data Bank Maintenance Center, and OBFS staff which provides systems support, in collaboration with the Principal Investigators. During the first stage of its operation the effort was focused on refining the uniform vocabulary and developing data collection methods. The second stage was a test phase during which the vocabulary and procedures for collection, entry and retrieval were implemented on a trial basis. Currently data are collected and entered, subject to a wide variety of data quality enhancement efforts. Preliminary analyses of the data collected in the first year are being performed and plans for final recommendations for a main phase are being formulated.

CONTRACT NARRATIVE
Office of Biometry & Field Studies, OD, NINCDS
Fiscal Year 1981

1. Univ. of Maryland (N01-NS-9-2302)
2. Univ. of S. Ala. (N01-NS-8-2397)
3. Duke Univ. (N01-NS-8-2396)
4. Boston Univ. (N01-NS-8-2398)

Title: Pilot Data Bank Network in Stroke

Contractors' Principal Investigators:
1. Dr. Thomas Price
2. Dr. Jay Mohr
3. Dr. Albert Heyman
4. Dr. Philip Wolf

Current Annual Level FY'81:
1. $141,000
2. 157,500
3. 139,000
4. 127,000

Objectives: The primary objective of this project is to develop a computerized interactive data bank network which will contain uniform, longitudinal data on stroke patients to aid both research and patient management. This is a collaborative project involving four separate medical centers which collect data, a data base management center to store and manipulate the data and staff at OBFS who have the responsibility for data analysis. This project has met its objectives and will continue into a full phase with competitive awards.

Major Findings: This project has produced a uniform vocabulary of data elements including test results, medical and surgical therapy, complications, and measures of stroke deficit and recovery. The collaborating hospital centers have collected data on approximately 1,000 stroke patients.

Significance to the NINCDS Program and Biomedical Research: The Pilot Data Bank Network in Stroke is important because it demonstrated the feasibility and utility of having medical centers collaborate to provide a resource of high quality data on the clinical course of stroke. This project will serve as a prototype for a national data bank network for other neurological disorders.

Proposed Course of the Project: The Pilot Stroke Data Bank Network is in the third and final year of its pilot phase. Data are being collected, examined for errors, and added to each data base. A "clean-up" phase will begin in August when all new patient acquisition will cease and the data collection will be focused on verifying follow-up status of surviving data bank patients, obtaining death information where necessary and correcting any omissions or errors which have been identified. Currently manuscripts describing the data bank and its findings are being prepared for publication, and several research studies are under way.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1981

Stanford Univ. (N01-NS-8-2390)

Title: Data Bank Maintenance Center for Pilot Data Bank Network Projects in Stroke and Traumatic Coma

Contractor's Project Director: Dr. James F. Fries

Current Annual Level FY'81: $202,453

Objectives: TOD-ARAMIS, recently renamed the "Data Bank Network", is the Data Bank Maintenance Contractor (DBMC) for the Pilot Projects to establish Data Bank Networks for Stroke and Traumatic Coma. During the three and one-half year contract period, the Data Bank Network system provides the host computer for these projects for data editing, storage, and retrieval, as part of the Time-Oriented Data Base (TOD) system. Data collected at pilot centers and entered into separately maintained Stroke and Coma data banks are available for retrieval within and among the pilot centers.

Major Findings: The Data Bank Network has created the computer schema for the Stroke and Coma Data Bank uniform vocabularies and developed methods for entering these data, as transmitted from the microprocessors located in each hospital, into the central data bank. The schema is a dictionary of data elements contained in the patient chart. Data entry personnel at the ten clinical centers have been trained and several retrieval programs have been developed and utilized for preliminary analyses and using standard statistical packages on the stored data.

Significance to the NINCDS Program and Biomedical Research: The Data Bank Maintenance Center is crucial to the success of the ten data banks which comprise the Pilot Data Bank Networks for Stroke and Traumatic Coma. It serves as the central data repository, maintains data integrity and provides programming and systems support to the ten centers. The availability of this database computer software has made these data bank networks feasible without extensive investment in new programming activity. Applying this system to stroke and traumatic coma is a first step in the development of an optimal system for a national data bank network for neurological disorders.

Proposed Course of Contract: The Maintenance Center is now focusing its activities on storage and retrieval for Stroke and Coma. The Coma data bank contractors have recently revised their vocabulary; the coma schema has been reconstructed to reflect the current vocabulary; and efforts are under way to transform existing data to the new format, where possible. Data are being entered at each center and are analyzed for errors by the automatic data check programs.

CONTRACT NARRATIVE
Office of Biometry & Field Studies, OD, NINCDS
Fiscal Year 1981

ARTHUR YOUNG & CO. (N01-NS-0-2326)

Title: Assessment of Data Bank Methodology

Contractor's Project Director: Dr. Craig Cook

Current Annual Level: $115,671

Objectives: The main purposes of this contract were to assess the effectiveness and utility of the present computer system, both hardware and software in use during the pilot phase of both Stroke and Traumatic Coma; and to compare the system to other presently available commercial and institutional systems. The contractor was then, if necessary, to recommend modification or replacement of software and/or hardware with a more suitable system. The contractor was also to survey the Stroke and Traumatic Coma principal investigators as to their needs for computerized administrative and patient management functions and to present the results of this survey as specifications to NINCDS.

Major Findings: The objectives of this contract have been realized and the findings have been presented to NINCDS in the form of interim and final reports.

Significance to the NINCDS Program and Biomedical Research: For most neurologic disorders there is a paucity of data for clinical research on the natural history of disease, on etiology, on the effectiveness of intervention and on methods of prevention. In order to provide longitudinal information, OBFS has undertaken the development of the Stroke and Traumatic Coma Data Base Systems. The pilot projects are utilizing existing computer software in order to concentrate resources on the problems of clinical data collection and to avoid the problems of introducing an unproven system.

Proposed Course of the Project: The study is completed and final reports have been submitted, reviewed, and accepted.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1981

WESTAT, INC. (N01-NS-6-2333)

Title: Nationwide Study of Stroke

Contractor's Project Director: Morton Robins

Current Annual Level: $ 0

Objectives: The primary objective of this survey was to produce national estimates and accompanying measures of precision for the incidence, prevalence, and economic costs of stroke. It was accomplished by devising and testing a method for carrying out the survey, and for presenting the statistical results of the survey.

Major Findings: After the data were collected a clinical algorithm was applied to the abstracted hospital records which classified the records according to type of stroke and degree of confirmation of the diagnosis in the medical records. Analyses were made relating the clinical data with the type of stroke and selected age-sex groupings. A series of articles containing the clinical, epidemiologic, and economic findings were written and published as a separate supplement to the journal Stroke.

Significance to the NINCDS Program and Biomedical Research: This survey is important for two reasons. First, it provides national estimates of the incidence, prevalence, and economic costs of stroke. These estimates are especially useful to NINCDS for purposes of program planning and allocation of funds. Second, the survey demonstrates to health investigators the value of probability sampling as a tool in sample selection. Probability sampling is the only general method available which can provide a measure of the precision of an estimate. Though this method is widely used in other areas, it is largely neglected in health studies. This survey and the others of the NINCDS Survey Program demonstrate that probability sampling is both desirable and feasible for certain types of health studies.

Proposed Course of the Project: The medical records were abstracted and pertinent information on the patient's demographic characteristics, the diagnostic categorizations of the stroke, date of onset, medical history of previous strokes or TIA's, clinical signs and symptoms, diagnostic findings, treatment, and outcome of hospital care were recorded for each stroke discharge selected in the sample hospitals. In addition, the hospital's business office was asked to furnish data on the direct medical charges to the patient or third party payer on those cases discharged during 1975. A subgroup of surviving patients (or close relatives) was also interviewed to obtain information on direct medical expenditures incurred during 1975 by the patient or the family. Additional facts on other aspects of economic impact of a stroke on the patient and the family were collected.

Moreover, for those discharged patients in the sample that were presumed to have had an initial stroke attack, their survival status was determined as of December 31, 1975, in order to calculate prevalence. The data collected in this survey were analyzed and the final report from the contractor was received. This contract is now completed. The final report has been reviewed and a series of articles containing the clinical, epidemiologic, and economic findings was written and published as a separate supplement to the journal Stroke in March/April 1981.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1981

RESEARCH TRIANGLE INSTITUTE (NO1-NS-4-2334)

Title: Survey of the Incidence, Prevalence and Costs of Head and Spinal Cord Injury

Contractor's Project Director: Dr. Daniel G. Horvitz

Current Annual Level: No cost to the Government.

Objectives: The chief aim of the NINCDS National Head and Spinal Cord Injury Survey was to develop estimates of incidence, prevalence, and economic costs for the United States population and selected subpopulations. These estimates were based on a sample of cases which have been selected using the techniques of probability sampling. These techniques are generally more expensive to use than other techniques of sampling but they offer the only general approach which permits the determination of levels of precision for the sample estimates. In this NINCDS survey, levels of precision were obtained for the major estimates of interest.

Major Findings: The objectives of this survey have been realized and the findings have been presented to NINCDS in the form of a final report. NINCDS staff have reviewed the contractor's final report and prepared a manuscript on major findings which was published as a supplement to the Journal of Neurosurgery (November 1980).

Significance to the NINCDS Program and Biomedical Research: The Head and Spinal Cord Injury Survey of NINCDS will have major impact on Institute programs in two distinct ways. First, the survey was designed as a tool for program planning. It provides an indication of the scope of the head and spinal cord injury problem as well as the economic costs (both direct and indirect costs) of the problem. With this information, and information from surveys of other disorders, program planners are better able to justify their research priorities and needs.

Second, this survey and others sponsored by NINCDS established that national surveys of relatively rare disorders can be feasible in certain instances using a case finding approach. This realization led to the development of a multipurpose survey which encompasses many disorders. The multipurpose survey will be a periodic survey in which estimates pertaining to various points in time (e.g., yearly, every five years) are obtained and analyzed for trends. This multipurpose survey will be major in scope and will have a significant impact on the programs of several NIH Institutes, the National Center for Health Statistics, and the Center for Disease Control.

Proposed Course of the Project: The study is completed and the final report has been submitted. A manuscript that will serve as the principal report on the project has been published.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1981

RESEARCH TRIANGLE INSTITUTE (263-78-C-0132)

Title: Case Verification and Supplemental HSCI Analyses

Contractor's Project Director: Mr. Paul Moore

Current Annual Level: No cost to the Government.

Objectives: After careful examination of the final report of the Head and Spinal Cord Injury Survey (Contract N01-NS-4-2334), it became evident that not all needed analyses had been anticipated and carried out prior to the expiration of the contract. The primary objective of this project is to undertake new analyses which will enhance the value of the monograph to be published on major findings from the survey. In addition, the algorithm which has been used in the main survey to determine medical eligibility for cases of spinal cord injury is to be evaluated in a small-scale specificity investigation.

Major Findings: NINCDS has received the new analyses and a report on the validity check.

Significance to the NINCDS Program and Biomedical Research: This project is of critical importance to NINCDS because the findings are needed for the major report on the Head and Spinal Cord Survey which will be published in a prestigious medical journal. The report will likely have a significant impact on the health care providers who have an interest in injuries to the head and spinal cord.

Proposed Course of the Project: All of the objectives of this project have been reached. The study has been completed.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1981

WESTAT, INC. (N01-NS-4-2336)

Title: Survey of Intracranial Neoplasms

Contractor's Project Director: Thomas G. McKenna

Current Annual Level: $ 0

Objectives: The primary objective of this survey is to produce national estimates and accompanying measures of precision for the incidence, prevalence, and economic costs of intracranial neoplasms.

Major Findings: The main survey has been completed and the findings have been presented to NINCDS by the contractor in the form of a final report. The report has been reviewed and additional data have been collected from the hospitals and certain analyses have been redone to improve the quality of the findings. The clinical, epidemiologic and economic findings will be presented in articles which will be submitted for publication in professional medical journals.

Significance to the NINCDS Program and Biomedical Research: This survey is important for two reasons. First, it provides national estimates of the incidence, prevalence, and economic costs of intracranial neoplasms. These estimates are especially useful to NINCDS for purposes of program planning and allocation of funds. Second, the survey will demonstrate to health investigators the value of probability sampling as a tool in sample selection. Probability sampling is the only general method available which can provide a measure of the precision of an estimate. Though this method is widely used in other areas, it is largely neglected in health studies. This survey, and the others of the NINCDS Survey Program, will demonstrate that probability sampling is both desirable and feasible for certain types of health studies.

Proposed Course of the Project: The main study has been completed and the final report was submitted by the contractor. After careful examination of the final report it became evident that certain ICDA categories needed to be examined in order to validate the findings before publication. Some of the participating hospitals furnished photocopies of selected patient records and the data has been reanalyzed. The clinical and epidemiologic findings have been prepared in an article which is ready to be submitted for publication in a neurological journal.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1981

NATIONAL ANALYSTS, INC. (N01-NS-4-2335)

Title: Survey of the Incidence, Prevalence, and Costs of Multiple Sclerosis

Contractor's Project Director: Beth Rothschild

Current Annual Level: $8500

Objectives: The primary objective of this survey is to produce national estimates and accompanying measures of precision for the incidence, prevalence, and economic costs of multiple sclerosis.

Major Findings: The prevalence of reported M.S. in the conterminous U.S. on January 1, 1976 is estimated to be 123,000 (a 95% confidence interval for this estimate is 106,000 to 140,000) for a rate of 57.8 per 100,000. Comparable figures for incidence indicate an average of 8,800 cases diagnosed annually between 1970-1975 (inclusive) for a rate of 4.2 per 100,000. The annual estimated cost of the disease is $810 million. The estimated cost to the existing population ranges from $12-28 billion depending on the discount rate employed.

Significance to the NINCDS Program and Biomedical Research: This survey is important for two reasons. First, it provides national estimates of the incidence, prevalence, and economic costs of multiple sclerosis. These estimates are especially useful to NINCDS for purposes of program planning and allocation of funds. Second, the survey will demonstrate to health investigators the value of probability sampling as a tool in sample selection. Probability sampling is the only general method available which can provide a measure of the precision of an estimate. Though this method is widely used in other areas, it is largely neglected in health studies. This survey, and the others of the NINCDS Survey Program, will demonstrate that probability sampling is both desirable and feasible for certain types of health studies.

Proposed Course of the Project: The project was completed and work has begun on the preparation of journal articles covering specific topics describing the M.S. population.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1981

UNITED STATES BUREAU OF THE CENSUS (Y01-NS-7-0031)
UNIVERSITY OF MISSISSIPPI (N01-NS-7-2357)

Title: Survey of Major Neurological Disorders in Copiah County Mississippi

Contractor's Project Director: Mr. Robert W. Mangold (Bureau of the Census); Dr. Armin F. Haerer (University of Mississippi)

Current Annual Level: $0 (Bureau of the Census); $0 (University of Mississippi)

Objectives: The primary objective of the proposal is to establish the prevalence of six major neurological and developmental disorders (cerebrovascular disease, convulsive disorders, cerebral palsy, psychomotor delay, Parkinson's disease, and dementia) in a well-defined population of southern blacks and whites. A secondary objective is to evaluate the sensitivity and specificity of certain screening questions by means of an item analysis at the close of the study. This analysis is needed because effective screening questions will be used in other morbidity surveys (e.g., the Health Interview Survey of NCHS).

Major Findings: Preparation of reports is continuing. Presentations are being scheduled for various professional meetings.

Significance to the NINCDS Program and Biomedical Research: At present, there are no adequate data on the prevalance of the six disorders of interest among southern blacks and whites in the United States. A number of studies suggest that stroke is more common among the black population. Mortality data and a few morbidity studies suggest that Parkinson's disease is less common among blacks. A biological explanation of this observation is that both melanin and dopamine are involved in the same metabolic pathway. Dopamine-deficiency in the basal ganglia has been found in patients with Parkinson's disease and is the rationale for the treatment of this condition with L-dopa. Blacks have a higher concentration of dopamine in the basal ganglia than whites which could explain a lower frequency of Parkinson's disease. On the other hand, it may be that blacks with this condition do not seek medical care or receive inadequate care. Mortality tabulations, with all of their biases, suggest that blacks have a predominance of epilepsy and cerebral palsy, but this requires confirmation with morbidity data. The magnitude of the dementia problem has not been studied in any United States population and Copiah County will provide some indication as to whether there is a racial and sex differential in the frequency of this group of conditions.

Proposed course of the project: The field operations for the main study were divided into two types of operations. The first was a household screening operation which was conducted by the Bureau of the Census. Residents of the study area were screened in their homes by means of a questionnaire administered by lay interviewers who were trained and supervised by the Bureau of the Census. The second type of operation was the examination of persons suspected of having one or more of the disorders of interest on the basis of responses given to questions from the screening questionnaire. The University of Mississippi provided senior, board-certified neurologists to accomplish the neurological examinations and to record the medical findings on forms designed especially for this study. After the close of field operations, the data were sent to the Bureau of the Census for processing. Staff of NINCDS, with the assistance of the Project Director from the University of Mississippi, are now analyzing the data and preparing scientific reports.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1981

RESEARCH TRIANGLE INSTITUTE (N01-NS-8-2383)

Title: Test of Study Design and Pilot Study for a National Survey of Epilepsy

Contractor's Project Director: Dr. Fred Bryan Jr.

Current Annual Level: $42,076

Objectives: This project was initiated to develop a new case finding approach for ascertaining the frequency of cases of epilepsy. The previously used methods have serious deficiencies, and this proposal seeks to remedy them. The goal is to use pharmacies which fill prescriptions for anticonvulsive drugs, to lead to the physicians providing care and thus to the epileptics. In a national survey, estimates of the scope of the epilepsy problem could be obtained for the U.S. population by using techniques of probability sampling.

Major Findings: The design test has been completed by the Contractor. The pilot study has begun and will continue until early next year.

Significance to the NINCDS Program and Biomedical Research: Morbidity surveys of relatively rare disorders are difficult to carry out for the U.S. population. One fundamental problem is that adequate numbers of cases for meaningful analyses may not be included in the sample of individuals selected for study due to stringent requirements for sampling a population. With epilepsy, the problem is compounded because of the perceived social stigma associated with having the disorder. The approach being tested in this contract will, if feasible, yield a cost-effective strategy for the sampling of epileptics who take anticonvulsive drugs. Furthermore, the privacy of the persons included in the study will be safeguarded to a great extent. If this strategy proves successful, a national survey of epileptics could be undertaken which would be invaluable to NINCDS and other organizations responsible for the planning of programs for epilepsy.

Proposed Course of the Project: The project is divided into two parts: a design test and a pilot study. The design test is on a small scale, and its chief purpose is to lead to the development of methodology for data collection from pharmacies and physicians and to aid in the design of the pilot study. The pilot study, which will be completed in November 1981, is on a larger scale, and its purpose is to resolve methodological issues which are raised by the investigators or were apparent after the design test. In addition, the pilot study will serve as a dry run for the procedures of the main survey. After the report on the pilot study has been studied carefully, a decision will be made on whether to embark on a national survey of epilepsy.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1981

WESTAT, INC. (N01-NS-7-2379)
NATIONAL CENTER FOR HEALTH STATISTICS (Y01-NS-7-0030)

Title: National Hospital Survey of Disease
(formerly Comprehensive Disease Statistics Survey)

Contractor's Project Director: Westat, Inc. - Dr. Anita Schroeder
NCHS - Dr. Monroe Sirken

Current Annual Level: Contractor - $ 0
NCHS - 25,000

Objectives: The objectives are to test the feasibility of obtaining hospital incidence and prevalence data for cases identified from abstracted hospital records of a number of neurological and other disorders, from a redesigned Hospital Discharge Survey of the NCHS. A key objective of a successful study would be to develop a survey program that would permit the annual collection of data on these disorders in order to develop trends of their incidence and prevalence.

The national sample of short-stay hospitals would provide a stable base for special studies. These studies would include methodological problems such as multiplicity. It would also provide an unbiased sample of patients, for periodic studies of special interest such as costs of illness, degree of disability, duration of illness, etc. Comparability of data collection methods, and protocols from the same sample of short-stay hospitals, would also permit comparison across disease lines.

Major Findings: The Feasibility Study has been being conducted in a sample of 27 hospitals. The data have now been analyzed and individual disease reports are being prepared, as well as the final report covering the methodological issues. NCHS has been involved in this cooperative effort with NINCDS and has worked on many methodological and statistical problems of the survey.

Significance to the NINCDS Program and Biomedical Research: NINCDS has been conducting a program of surveys of neurological disorders. There is a need to consider a more comprehensive approach to the collection of disease statistics. First, there is a considerable degree of redundancy in the present approach, both within NINCDS, and, probably, across Institute boundaries. Redundancy leads to higher than necessary costs associated with the collection of disease statistics data. Second, the present approach leads to delays in obtaining current information, since there are a limited number of surveys which can be conducted at any one time. Third, the methods and protocols used by each contractor differ and this affects the comparability of data across disease lines. Fourth, and perhaps most important, these data provide planning information based on a limited time period, when in fact trend data, obtained on an annual, prospective basis, would better serve the program planning and program evaluation functions.

The development of a comprehensive system for the collection of disease statistics on a wide variety of diseases would be of great value to NINCDS and other NIH Institutes, for it would eliminate the four above-mentioned major problems.

This proposal would establish a cooperative and joint relationship between NCHS and NINCDS, and would provide for an NCHS collection of national health statistics of considerable interest to NINCDS, and potentially, to other NIH Institutes. It would, to the extent that incidence and prevalence data can be obtained from records at short-stay hospitals, supplant NINCDS data collection efforts. NINCDS would continue to analyze the data collected to meet its own program planning needs.

Proposed Course of the Project: In the Feasibility Study the contractor was responsible for the field work, data collection, and processing of the data. The disease algorithms were prepared by NINCDS staff with the aid of medical consultants and other participating NIH Institutes. The development of the sampling plan, counting rules, and selection of the participating hospitals was undertaken by the National Center for Health Statistics, under a separate interagency agreement.

After the final report of the Feasibility Study has been received and reviewed, a determination will be made as to what will be the next steps leading to the main National Study.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1981

NATIONAL INSTITUTE OF MENTAL HEALTH (1Y01-0-0004-00)

Title: ECA Dementia Supplement

Contractor's Project Director: William Eton, Ph.D.

Current Annual Level: $165,000.

Objectives: The study will identify a group of demented individuals who are non-institutionalized and the type of dementia will be ascertained by means of a medical examination. An estimate of the social and economic costs will also be generated.

Major Findings: None. The data are still being collected.

Significance to the NINCDS Program: As the population of this nation ages, the dementias will become an increasing medical problem. There are currently no reliable data on the cost of these disorders and this information is needed to assist in future health planning efforts.

Proposed Course of the Project: This project is an add-on to an existing NIMH program of mental health surveys. After an initial screening for cognitive disability, the subjects who are disabled will be given a medical examination. A close relative or friend of those with verified dementias will be used to help establish the history of the disease and estimate the social and economic costs to the affected individual and their friends or relatives.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02450-02 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)
Spinal Manipulative Therapy as Treatment for Musculo-Skeletal Dysfunction in Athletes formerly titled "Study of Efficacy of Spinal Manipulative Therapy on the Performance of Athletes"

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Peter Jokl, Assoc. Prof. of Orthopaedic Surgery, Director of Athletic Medicine, Yale University School of Medicine
Murray Goldstein, Acting Director, National Institute of Neurological and Communicative Disorders and Stroke, NIH
J.F. McAndrews, President, Palmer College of Chiropractic
William Weiss, Chief, Office of Biometry & Field Studies, NINCDS

Other: James M. Dambrosia, Mathematical Statistician, Office of Biometry and Field Studies, NINCDS

COOPERATING UNITS (if any)
Yale School of Public Health

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0

CHECK APPROPRIATE BOX(ES)
☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER
☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project will evaluate the efficacy of spinal manipulative therapy for alleviating neuromuscular and musculo-skeletal problems that diminish athletic performance. A demonstration of the effectiveness of treatment will be provided by a randomized controlled clinical trial of student athletes at Yale University. The OBFS role in this project's responsibility is the design and analysis of the trial to be accomplished in close collaboration with the Yale University School of Medicine.

PHS-6040
(Rev. 2-81)

Project Description:

Objective: The general objective of this study is to determine the effectiveness of spinal manipulative therapy as treatment for neuromuscular and musculo-skeletal dysfunctions that diminish the performance of athletes. During the course of a pilot study, eligibility requirements and consistent reproducible diagnostic criteria will be established, a study protocol will be written, and outcome measures will be developed for use in the clinical trial.

Methodology: The method of treatment evaluation is a randomized controlled clinical trial of spinal manipulation versus standard medical care. The study has two components: (a) the pilot phase and (b) the clinical trial. The pilot phase of the study will provide information as a basis for the design of the clinical trial. Appropriate analysis of both the pilot data and the trial data will be accomplished by OBFS in collaboration with Yale University. Quality control, including periodic monitoring of the ongoing trial, will be included as part of the study design. Currently, a full factorial design is the proposed statistical model to be implemented for the study.

Major Findings: Reliability and reproducibility of diagnostic findings by manipulative specialists have not yet been determined. Definition of outcome measures is a difficult problem, which may be alleviated by the use of strength measuring equipment, e.g., Cybex. Success of the study is most likely if it is conducted at a single center under the guidance of a single person.

Significance to NINCDS and Biomedical Research: At present, conclusions regarding spinal manipulation cannot be derived from the literature. Recent studies generally fail to demonstrate efficacy except as interesting trends. This study should provide some definitive answers regarding the effectiveness of spinal manipulation in athletes.

Proposed Course: Yale University will submit a grant proposal for the clinical trial to NIH. Contingent on NIH approval, the study will begin in FY'82 with completion expected 1 1/2 years after initiation.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02497-01 OBFS

PERIOD COVERED
October 1, 1980 to September 31, 1981

TITLE OF PROJECT (80 characters or less)

INDO-U.S. Study of Head Injury

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI's:
William Weiss, Chief, OBFS, NINCDS
Dr. John Jane, Chairman, Dept. of Neurological Surgery, Univ. of VA, Charlottesville, VA
Dr. Prakash Tandon, Chairman, Dept. of Neurosurgery, All-India Institute for Medical Research, New Delhi, India

Other:
Rebecca Rimel, R.N.N.P., U. of VA, Charlottesville, VA
Cynthia Gross, Ph.D., Biostatistician, CAS, OBFS, NINCDS

COOPERATING UNITS (if any)

University of VA, Dept. of Neurosurgery, Charlottesville, VA
All-India Institute of Medicine, New Delhi, India

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS: .15	PROFESSIONAL: .10	OTHER: .05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Information on head injured persons has been collected in independent research efforts in Charlottesville, Virginia, and in New Delhi, India. A preliminary review of these data collection efforts has indicated significant overlap in the type of information collected. A preliminary analysis of the collected data is proposed to identify differences and similarities between these head injured populations, and to determine the feasibility of a prospective cooperative association for the study of head injuries.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: Data have been collected on 1500 head injury patients in Charlottesville, Virginia, during 1977 and 1978, and an equal number of head injury cases in New Delhi, India. Differences and similarities in etiology, treatment, and outcome of head injuries will be evaluated to determine the feasibility of a prospective comparative study.

Methodology: The Charlottesville data are accessible on computer tape, while similar data at the All-India Institute remain uncoded. These data will be coded and computerized in a manner that is compatible with the Charlottesville data. Detailed comparative analyses of the two sets of data will then be performed.

Significance to NINCDS Program and Biomedical Research: Severe head injury is a common cause of death and disability. Extensive emergency and acute care hospital services must be devoted to these patients, as well as rehabilitation and chronic care services for survivors. Head injuries are a major problem both in the developed countries of the west and in developing countries. Comparing head injuries, their treatment, complications and outcome from centers in the United States and India will further the understanding of this important problem.

Proposed Course of Project: This study is under review by an Indian Research Board, and, if approved, would require approximately 1 1/2 years for completion.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02506-01 OBFS

PERIOD COVERED October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Antibody Titers in Macacas on Cayo Santiago

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: William T. London, Chief, Experimental Pathology Section,
IDB, IR, NINCDS

Other: William Weiss, Chief, OBFS, OD, NINCDS

COOPERATING UNITS (if any)

Infectious Diseases Branch, IR, NINCDS

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland, 20205

TOTAL MANYEARS: .05	PROFESSIONAL: .05	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project will provide a test of four antigens on adult and juvenile macacas on Cayo Santiago, Puerto Rico. One problem is to determine the percent of positive antibody titers that can be determined from the adult sample for whom blood sera are presently available, and the number of juveniles that should be sampled.

PHS-6040
(Rev. 2-81)

Project Description:

Objective: To test four antigens on adult and juvenile macacas from colonies on Cayo Santiago, Puerto Rico. The initial statistical problem is to determine, from the sera of the adult macacas already available, the lowest proportion of positive antigens that can be determined with high probability; and the number of juvenile samples that should be collected to assure that levels of positive antibodies will be identified when certain proportions of samples positive antibodies are present in juvenile macacas.

Methodology: The "f" distribution is used as an approximation to the hypergeometric distribution for estimating the probabilities of interest.

Major Findings: Work is progressing on the analysis of the sera for antibody levels for four antigens.

Significance to NINCDS and Biomedical Research: This project will determine whether macaca colonies can exist free of these viral antibodies.

Proposed course: Continuing

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02310-05 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

A Statistical Study of a Sensory-Decision-Theory Method in the Measurement of Experimental Pain

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBFS, NINCDS

Other: Joseph Yang, M.D., Research Anesthesiologist, Department of Anesthesiology, Columbia University
Crawford Clark, Ph.D., Research Psychologist, N.Y. Institute of Psychiatry

COOPERATING UNITS (if any)

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .05	PROFESSIONAL: .05	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project investigates statistically the nature of a sensory-decision-theory (SDT) method in determining pain components from responses of experimental subjects to painful stimuli. Both parametric and non-parametric approaches to the SDT method were evaluated for the estimability of, and the relationship between, sensory discriminability and response bias. Sampling behavior of these indices was also examined. A report summarizing the results of this study is in preparation.

Project Description:

Objective: To investigate statistically the nature of a sensory-decision-theory (SDT) method in determining pain components from responses of experimental subjects to painful stimuli.

Methodology: Both parametric and non-parametic approaches to the SDT method were evaluated for the estimability of sensory discriminability and response bias. Sampling behavior of these two indices was also examined.

Major Findings: The results of this investigation indicated that the response bias, either estimated by a parametric or a non-parametric SDT method, is not statistically independent from sensory discriminability. In a comparative experiment, the difference in response bias will reflect the true difference (or change) in response bias between two compared groups only if sensory discriminability is not significantly changed. Therefore, the meaning of the difference in the estimates of response bias in a comparative experiment must be interpreted with caution in conjunction with the meaning of the difference between sensory discriminabilities. A report to summarize the results of this investigation is in preparation.

Significance to NINCDS Program and Biomedical Research: Measurement of pain is a problem that has long confronted pain investigators. The SDT method of determining pain components is one of several methods introduced to the field of pain research in recent years. However, the validity of this technique has not been clearly examined. The present study clarified one aspect of the controversial problem of the SDT method in the measurement of pain.

Proposed Course of Contract: This study is concluded. Collaboration with investigators associated with the Department of Anesthesiology, Columbia University, in a laboratory test to confirm the statistical findings is pending. The report of this study will be submitted for publication.

Publication: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02342-04 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Associations of Multiple Sclerosis with Certain Serological Parameters

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBFS, NINCDS

COOPERATING UNITS (if any)

Reed Neurological Center, UCLA

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0	0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Association of serological parameters such as I_gG, I_gM, Measle HI and EBV titers with different types of multiple sclerosis were investigated statistically. Significant differences in these serological measurements were observed between each type of multiple sclerosis and the control sample. Furthermore, the patterns of the serological difference vary among types of multiple sclerosis. The results of this study will be reviewed by an investigator of the Reed Neurological Center, UCLA. The attempt to obtain more data from different sources was not successful. No further work in this area is anticipated.

PHS-6040
(Rev. 2-81)

Project Description:

Objective: To investigate the association of several serological parameters with different types of multiple sclerosis.

Methodology: Serological data such as I_gG, I_gM, measle HI, and EBV titers of 86 multiple sclerosis patients classified as relapse, relapse-progressive, and progressive types were obtained from the Reed Neurological Center of UCLA for this study. Multivariate statistical techniques were employed in the investigation.

Major Findings: Significant differences in titers and levels of these serological parameters were observed between each type of multiple sclerosis and the control sample. Furthermore, the patterns of the significant differences vary among different types of multiple sclerosis. A report of this study will be sent to Dr. G. Ellison of the Reed Neurological Center for further review.

Significance to NINCDS Program and Biomedical Research: Further investigation of a broad base of data is needed to test the association of these serological parameters with different types of multiple sclerosis. Future investigations may lead to refinements of the classification of multiple sclerosis.

Proposed Course of Contracts: The attempt to obtain more data from different sources was not successful. No further work is planned.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02504-01 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Estimation of the Incidence Rate of Disabling and Severe Headache

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBFS, NINCDS

P.I.: Murray Goldstein, D.O., M.P.H., Acting Director, NINCDS

COOPERATING UNITS (if any)

Dewey K. Ziegler, M.D., Department of Neurology, University of Kansas

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.2	.2	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The data used in this study involved the age of onset of disabling and/or severe (D/S) headache. Subjects were identified from a survey of a midwest non-clinical population which was conducted by the University of Kansas Department of Neurology. A mathematical procedure was derived to estimate the incidence rate and the age-specific incidence rates of D/S headache in that population. The validity of these estimates was examined in conjunction with the data on prevalence and on length of illness of headache existing in the published medical literature, and the relationship among these epidemiological indices. A report of this study is in preparation.

PHS-6040
(Rev. 2-81)

Project Description:

Objective: To estimate the incidence rate of disabling and/or severe (D/S) headache based on data of age of onset of D/S headache in a nonclinical population.

Methodology: The life history of headache of 1809 subjects was recorded from a survey of a midwest nonclinical population conducted by the University of Kansas Department of Neurology. The data include the age of onset of D/S headache. (The definition of D/S headache follows Ziegler et al., Neurology 27: 265-269, 1977). A mathematical procedure was derived to estimate the incidence rate as well as age-specific incidence rates of the D/S headache of that population. The validity of these estimates was examined with the prevalence rate data and the length of illness of headache existing in the published literature, as well as the relationship among these epidemiological indices. A discussion of the results of the study will also involve the aspect of self-limitation of migrainous headache. A report of this study is in preparation.

Major Findings: The annual incidence rate of D/S headache was estimated to be 1.3 new cases per 100 persons in a nonclinical population. Age-specific incidence rates indicate that the highest incidence of D/S headache occurs at ages between 15 to 25 years (4.8 cases per 100 persons). The incidence rate decreases to 2.1 cases per 100 persons at ages between 25 to 40 years. After 40 years of age the incidence rate of D/S headache dropped sharply to less than one case per 100 persons, and after 65 years of age, in only one case per 1000 persons would a D/S headache be reported.

Significance to NINCDS Program and Biomedical Research: Headache is of interest to the NINCDS Program. Epidemiological information on incidence of D/S or other types of chronic headache in a general population has been totally absent from the medical literature. The present study provided a reasonable estimate of the incidence rate of D/S headache.

Proposed Course of Contract: The report of this study shall be submitted for publication.

Publication: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02505-01 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Headache in Pregnant Women

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBFS, NINCDS
P.I. Murray Goldstein, D.O., M.P.H., Acting Director, NINCDS

COOPERATING UNITS (if any)

Paul Nichols, Ph.D., Developmental Neurology Branch, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .1	PROFESSIONAL: .1	OTHER:

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project investigates the relationship between pregnancy and migrainous headache based on the data recorded from a large group of women in pregnancy -- the Collaborative Perinatal Project gravida. Subgroups of pregnant women characterized by the absence and presence of migraine and other recurrent headaches prior to or during pregnancy will be identified. Characteristics of these subgroups will be described and compared on a variety of demographic, sociological, medical and gynaecological factors, and the associations of headache with other diseases. The subgroup of women who have a past history of migraine, but who reported absence of headache during their pregnancy will be studied.

PHS-6040
(Rev. 2-81)

Project Description:

Objective: To investigate the relationship between pregnancy and migrainous headache -- an etiological problem which has long been of interest to headache investigators and clinicians, and to describe the characteristic profiles of women in pregnancy, with or without this type of headache, from a large group of pregnant women.

Methodology: The Collaborative Perinatal Project (CPP), has collected extensive maternal information from a non-selected group of approximately 60,000 women, prior to and during pregnancy. Information about headache and migraine, and medications used by the headache-suffering women were also recorded. The present study carries out statistical investigations with CPP data. Subgroups of pregnant women will be identified who were characterized by the absence or presence of migraine and other recurrent headaches prior to or during pregnancy. Characteristics of these subgroups will be described and compared on a variety of demographic, sociological, medical and gynaecological factors and the association of headache with other diseases. The subgroup of women who have a past history of migraine but reported absence of headache during their pregnancy will be studied.

Major Findings: A preliminary investigation of the CPP data indicated a rather high percent of women who had headache frequently during their pregnancy. However, for this study, an effort must be made to sort out the cases who only had occasional headache only before meaningful subgroups can be derived.

Significance to NINCDS Program and Biomedical Research: Headache is an area of interest to the NINCDS Program. Epidemiological findings on the relationship between pregnancy and headache can be useful to clinicians in the management of the headache problem for pregnant women. The present study, based on a very large, non-selected sample of pregnant women in the United States, will yield this type of information.

Proposed Course of Contract: A detailed plan for this study will be prepared.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02443-02 OBFS

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Development of Offline Data Entry System for Stroke and Coma Projects

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Barbara Nichols, Programmer, CAS, OBFS, OD, NINCDS

Other: Selma C. Kunitz, Head of Computer Applications Section, OBFS, OD, NINCDS.

COOPERATING UNITS (if any)

LAB/BRANCH Office of Biometry and Field Studies

SECTION
Computer Applications Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	.8	.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A "front end" general purpose software package was enhanced for the Data-point terminals for the Data Bank Centers, which allows data to be entered, edited and stored locally by time and date. The software operates with menu processing, in which a nonprogrammer can choose the option for data entry from a list. It produces screen images which replicate the order of data on the data collection record. During data entry, data are edited for valid numeric ranges, alpha/numeric checks, code lists, and special formats such as dates. A new communication discipline is being added to insure the accuracy of data transmission. Patient management reports were designed and are now being implemented to serve as tools for patient care at the Databank Network Centers.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To provide the medical Databank Networks with a tool to allow easy entry, updating and transmission of patient data to the Data Bank Maintenance Center. To meet the needs of hospital patient care management at the Data Bank Network Centers.

Methodology: The front-end software is being developed and implemented during two national pilot data bank studies in Stroke and Traumatic Coma. Its effectiveness in meeting the needs of the Data Bank Centers is being evaluated during this period.

Major Findings: The studies have yielded over 1400 patients in the two Data Banks. New procedures are being developed and will be implemented to enhance the front-end capabilities.

Significance to Biomedical Research and the Program of the Institute: The front-end is an intregal part of the National Data Bank Projects, which were established to collect and maintain medical data for both patient management and clinical research.

Proposed Course of the Project: Continuation of development during the main phase of the Stroke and Traumatic Coma Data Bank Studies.

Publications: Nichols, B.J., Rush, R.L., Edelstein, S.L., Fishman, I., Kunitz, S.C. Data Entry for Multiple Center Databanks - A Microprocessor Approach. Fifth Symposium on Computer Applications in Medical Care. In press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER ZO1 NS 02408-03 OBFS

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Clinical Databanks As a Resource for Epidemiologic Research

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Cynthia Gross, Ph.D., Biostatistician
Computer Applications Section, OBFS, OD, NINCDS

Other: Selma C. Kunitz, Head, Computer Applications Section,
OBFS, OD, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section, OBFS, OD, NINCDS

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.3	.3	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Much has been written on the use of observational studies in epidemiological research. It will be necessary to apply many of the same epidemiologic techniques used in conventional observational studies to the clinical data bank. Work on determining which epidemiologic approaches are most appropriate for use with clinical data banks has begun in conjunction with the Stroke and Traumatic Coma Databank Networks (NO1-NS-8-2309, 6, 7, 8, NO1-NS-9-2302, 96, 97, 98). A presentation at the Society for Clinical Trials was based, in part, on the work of this project.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To identify and evaluate current epidemiological methods and determine which are appropriate for use in observational, multicenter clinical data banks.

Methodology: This is an ongoing review of current epidemiological and biostatistical literature on methods for conducting and analyzing observational studies. Areas of special interest include pooling data, matching of controls and quality assurance techniques. Where appropriate these methods have been explored using the collected data of the Stroke and Traumatic Coma Data Banks (Z01 NS 02238-05 OBFS and Z01 NS 02340-04 OBFS).

Major Findings: Presently, the impact of pooling data across centers is being studied and statistical adjustments for differences are being explored.

Significance to NINCDS Program and Biomedical Research: The data bank methodology is being utilized for research on the clinical course of certain neurological disorders where, due to the present state of knowledge, ethical or logistical reasons more experimental techniques such as clinical trials are not presently feasible. This is an important project to insure the quality and accuracy of the data being collected and the appropriateness of conclusions drawn.

Proposed Course of Project: The Stroke Data Bank has recently been approved for a main phase of 3-5 years and this project will continue in conjunction with it.

Publications: Kunitz, S.C., Gross, C.R. and Heyman, A. "Databanks and Clinical Trials: From Adversaries to Complementary Tools" presented to the Society for Clinical Trials, May 1981, San Francisco. To be submitted for publication.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02407-03 OBFS

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Assessment of Databank Methodology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Sylvia Edelstein, Computer Systems Analyst, CAS,
OBFS, OD, NINCDS

Other: Selma C. Kunitz, Head, Computer Applications Section
OBFS, OD, NINCDS

COOPERATING UNITS (if any)

Arthur Young & Co., Washington, D.C.

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.7	.5	.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A project to assess the computer methodology used in the Pilot Data Bank networks in Stroke and Traumatic Coma was implemented. Its purpose was to 1) compare the methodology in these pilots to other available data base management systems, 2) develop specifications for modifying or replacing all or part of the current system, (TOD), in order to obtain a more optimal system, and 3) survey the users of the front-end Datapoint system to determine their need for computerized administrative and patient management reports, and prepare sample designs to satisfy this function.
This project has been completed.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: The objectives were to assess the effectiveness and utility of the present computer hardware and software used in the pilot phase of the Data Bank projects in Stroke and Traumatic Coma; to compare this system to other available commercial and institutional systems; to make recomendations, if necessary, for modifications or replacements of the software/hardware with a more suitable system; and to determine the needs of the users of the front-end Datapoint system for computerized administrative and patient management reports.

Methodology: The following activities were performed to collect the necessary data to perform the assessment: Interviews with team members at Stroke and Traumatic Coma sites, and a survey of their needs; meetings with management, biostatisticians and programmer-analysts in NINCDS; review of pertinent literature, and study of the hardware and software currently used with this project. There were also meetings and phone conversations with vendors, universities, and individuals familiar with alternative medical data bank systems.

To determine the needs of the front-end user for administrative and patient management tools, a survey was done to elucidate their needs for such reports, as well as the content and style of each output.

Major Findings: It was recommended that this office continue with the hardware and software configuration currently used. Enhancements to the current data bank network were identified such as: the alteration of the "visit" concept, changes in selected statistical routines, increased administrative and and patient reporting capability on the front-end mini-computer.

Significance to NINCDS Program and Biomedical Research: This study provided ideas and detailed specifications for improvements in current computer system. It also contains many evaluations which are needed to assess any other computer system which may be considered in the future. A successful, fully functional computer system is necessary to satisfy NINCDS' objective for the clinical data banks: to provide clinician's with the tool to collect, store, and retrieve pertinent patient information in order to advance research and aid patient management.

Proposed Course of Project: This project has been completed.

Publications: None.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02498-01 OBFS

PERIOD COVERED October 1, 1980 to September 31, 1981

TITLE OF PROJECT (80 characters or less)

CT Scan Observer Variability Study

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Cynthia Gross, Ph.D., Biostatistician, CAS, OBFS, NINCDS
Other: James Dambrosia, Ph.D., Mathematical Statistician, SMS, OBFS NINCDS
Karlin Richardson, Programmer, CAS, OBFS, NINCDS
Dr. Thomas Gennarelli, Neurosurgeon, Univ. of Penn. School of Medicine

COOPERATING UNITS (if any)

University of Pennsylvania, School of Medicine

LAB/BRANCH Office of Biometry and Field Studies

SECTION Computer Applications Section

INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS: .15	PROFESSIONAL: .10	OTHER: .05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A study of observer variability in CT Scan reading and coding was implemented utilizing identical sets of CT Scan polaroids and the CT Scan Data Collection form of the Pilot Traumatic Coma Data Bank. Readers were neurosurgeons participating in the Coma Data Bank (Z01 NS 02340-03 OBFS). The degree of agreement among readers was calculated by Kappa statistics and an item analysis was performed. Severity of errors was determined by a substantive analysis.

Project Description:

Objectives: To measure the amount of inter-observer agreement in the utilization of the Traumatic Coma Data Bank CT Scan Form.

Methodology: Neurosurgeons at each Traumatic Coma Data Bank Center received identical sets of polaroids from eleven CT scans of head injured patients. No serial scans were included and each set contained between two and eight photographs. Each neurosurgeon completed a CT Scan data form for every case by "usual data bank procedures". In some cases this included consultation with a neuroradiologist prior to coding. There were eight observers in all.

Major Findings: Each of the 30 items on the CT Scan form was analyzed for degree of agreement above chance. The proportion of agreement on some items, such as "Bone Lesions" and "Intraventricular Blood" was very high, while other items such as "Brain Stem Cisterns" had lesser degrees of agreement. The results were reviewed by a neurosurgeon who identified systematic errors and discriminated substantive errors from clinically insignificant variation.

Significance to NINCDS Program and Biomedical Research: CT Scanning is a major diagnostic tool which because of its speed and non-invasive nature allows rapid evaluation of traumatic head injuries prior to surgery. As a data source for clinical research CT Scan findings are considered "hard" data, yet, since the information must be coded observer/coder variability is inevitable. This study is one of the first which has attempted to quantify agreement among CT Scan readers.

Proposed Course of Project: One set of comparative readings has been collected and the data analyzed. The results of this analysis have been used to revise the CT Scan Form used in the Pilot Traumatic Coma Data Bank. Current plans include further biostatistical research in the measurement of inter-observer agreement, additional data analysis, and publication of results from this study.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02499-01 OBFS

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Stroke Incidence in South Alabama

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Cynthia Gross, Ph.D., Biostatistician, OBFS, NINCDS
Dr. Jay Mohr, neurologist, University of S. Alabama College of Medicine
Dr. Carlos Kase, neurologist, University of S. Alabama College of Medicine.

COOPERATING UNITS (if any)

University of South Alabama, College of Medicine, Mobile, Alabama

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS: .30	PROFESSIONAL: .25	OTHER: .05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

As a component of the Pilot Stroke Data Bank (N01 NS 8-2397), 1980 stroke incidence data has been collected for the population of a well-defined geographic area located in three counties in southern Alabama. These data provide incidence rates by age, sex, race, and stroke type. Medical history as well as other factors were collected for each stroke case. These data are presently being analyzed for a publication which will compare these findings with other similar studies of stroke.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To determine the incidence of stroke in a well-defined population located in the "Stroke Belt" of the southeastern United States; to calculate stroke incidence rates by age, race, sex and type of stroke; to examine these rates for differences; and to identify factors related to these differences which may be of etiological significance.

Methodology: The study area consisted of portions of Mobile County, Alabama, and Baldwin County, Alabama and Monroe County, Alabama, in its entirety. All residents of the study area who had a stroke in 1980 and were hospitalized were identified by a surveillance of nine hospitals located within or adjacent to the study area. As a component of the Pilot Stroke Data Bank in south Alabama, data were collected for each case with respect to demographic information medical history, stroke course and outcome. The 1980 census data were used to determine the population for the calculation of rates.

Major Findings: The data have been analyzed in a preliminary fashion since a few additional cases are still being added to the study group. These preliminary analyses showed that age adjusted incidence rates were higher for blacks than for whites. The age specific rates were highest for black females. Over 60% of the stroke cases had a history of hypertension and about 20% had a history of diabetes. There was some variation in these histories by type of stroke. No seasonal trend was seen.

Significance to NINCDS Program and Biomedical Research: Stroke is the third leading cause of death in the United States and in many developed nations. While stroke mortality rates have been declining there are currently insufficient data to determine if stroke incidence is being reduced in all sex/race groups and for all types of stroke. While the planned two years of this study will not provide extensive data on time trends, it will provide a point of comparison to earlier studies, and more importantly, since this is one of the few stroke epidemiology studies to have extensive diagnostic data including CT Scan data, it will provide valuable comparisons to future studies in this area.

Proposed Course of Contract: A "clean-up" phase of 1980 has begun which includes 1) review of hospital discharge records to identify cases missed during the prospective accrual of patients and 2) review of death certificates for 1980 resident stroke deaths to also identify missed hospital cases and non-hospitalized deaths. The data collection for 1981 continues.

Publications: Gross, C.R., Kase C.S., Shear, C.L. and Mohr, J.P. "Stroke Incidence in South Alabama". Presented to the Society of Epidemiological Research meeting, June, 1981, to be submitted for publication.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02500-01 OBFS

PERIOD COVERED October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Polymyositis/Dermatomyositis Study

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Irene G. Fishman, Statistician, CAS, OBFS, OD, NINCDS
Selma C. Kunitz, Chief, CAS, OBFS, OD, NINCDS

Other: Ken Elsner, Systems Analyst, CAS, OBFS, OD, NINCDS

COOPERATING UNITS (if any)

Christopher Clark, M.D., Elliott Neurological Center
of the Pennsylvania Hospital, Philadelphia, PA

LAB/BRANCH Office of Biometry and Field Studies

SECTION Computer Applications Section

INSTITUTE AND LOCATION NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .3	PROFESSIONAL: .3	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (X) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The low incidence of myositis and its chronic course necessitates collaboration of a number of investigators. The project involves consultation by OBFS staff to a group of neurologists who are considering the possibility of collecting clinical information on myositis patients. An initial set of data items for collection has been proposed and forms were designed to enter data on demographic information, initial evaluation, and subsequent follow-up. These forms have been distributed to interested researchers and are being tested through actual use. A meeting is planned in September to discuss possible refinements of the forms and research objectives.

Project Description:

Objectives: To provide a group of extramural investigators with expert advice in order to permit them to devise a system for collecting clinical information on patients with polymyositis/dermatomyositis, prospectively from multiple investigators. This study may provide information regarding the response of myositis to currently employed therapies. In addition, it would be useful to identify subgroups of myositis that might have a common etiology and clinical course.

Methodology: Forms have been designed to collect clinical data on demographics, initial examinations and follow-up examinations. These forms have been distributed to participating neurologists and data is presently being collected.

Significance to NINCDS Program and Biomedical Research:

One of the major difficulties with evaluating the questions of efficacy of therapy in myositis is the lack of objective prospectively collected data which could be used to determine how well patients are doing in the present therapeutic climate. Because of the low incidence of the disorder and its chronic course, multicentered data collection is needed. The application of present knowledge of data base technology to this problem is particularly useful.

Proposed course: The project is in its initial stages. A meeting to evaluate the present forms is to be held in Fall, 1981. OBFS will continue only in a consultative role.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02501-01 OBFS

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Myasthenia Gravis Study

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Irene G. Fishman, Statistician, CAS, OBFS, OD, NINCDS
Selma C. Kunitz, Chief, CAS, OBFS, OD, NINCDS

Other: Ken Elsner, Systems Analyst, CAS, OBFS, OD, NINCDS

COOPERATING UNITS (if any)
Christopher Clark, M.D., Elliott Neurological Center of the Pennsylvania Hospital, Philadelphia, PA.

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .1	PROFESSIONAL: .1	OTHER:

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The project involves consultation to a group of neurologists who are interested in the possibility of collecting clinical information on patients with myasthenia gravis. An initial set of parameters to be collected has been proposed and a first version of forms has been designed, to enter demographic, initial evaluation, and subsequent follow-up data. This project is currently in progress. OBFS staff is acting only in a consultative role to this extramural group of investigators.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To provide extramural investigators with expert advice in order to permit them to devise a system for collecting prospective clinical information on patients with myasthenia gravis.

Methodology: Forms have been designed to collect demographic information and clinical data on initial and follow-up examinations of patients with myasthenia gravis. These are currently being evaluated for future distribution.

Significance to NINCDS Program and Biomedical Research: One of the difficulties in evaluating various therapeutic strategies for the treatment of neuromuscular disorders is their low incidence. Multicenter data need to be obtained, and collected via standardized forms and methods, in a prospective way. In addition, a common protocol needs to be developed to evaluate the status of individual patients, especially in defining severity of the disease in a universally acceptable manner. The application of current data base technology to the storage, retrieval, and evaluation of clinical information is particularly useful in this case.

Proposed Course: The project is in the initial stage and OBFS staff acts only in a consultant capacity.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02493-01 OBFS

PERIOD COVERED October 1, 1980 to September 31, 1981

TITLE OF PROJECT (80 characters or less)

Stroke Diagnosis: The NINCDS Data Bank Algorithm

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI's: Selma Kunitz, Head, Computer Applications Section, OBFS, NINCDS
Jay P. Mohr, Neurologist, University of S. Alabama College of Medicine
Carlos Kase, Neurologist, University of S. Alabama College of Medicine
Cynthia Gross, Ph.D., Biostatistician, CAS, OBFS, NINCDS
James Dambrosia, Ph.D., Mathematical Statistician, SMS, OBFS, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Computer Applications Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS: .15	PROFESSIONAL: .15	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In conjunction with the NINCDS Pilot Stroke Data Bank Network (Z01 NS 02238-05) a diagnostic classification schema for strokes was devised which consisted of of cerebral pathology, vascular pathology, location, diagnostic source and diagnostic role. Approximately 1,000 stroke patients have been classified by this algorithm and the results are being analyzed for publication.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To devise a classification algorithm for stroke diagnosis which would incorporate the degree of laboratory evidence supporting the diagnosis as well as allow multiple investigators to apply clinical judgment for classification in a consistent manner across centers to provide reliable data for research.

Methodogy: A comprehensive list of criteria for each stroke type was developed, with diagnostic source levels to indicate the degree of laboratory support for the diagnosis. A diagnostic role variable indicates the importance of the diagnosis to the present clinical syndrome. Major classifications of infarction include atherothrombotic infarctions, embolic infarctions, lacunes, and infarction of unknown origin. To monitor the ability of multiple investigators to consistently apply these algorithms, a procedure of distributing identical case records for "blind" and independent coding termed "recycling" has been implemented.

Major Findings: Comparisons among investigator readings on the "recycling" have indicated areas of high agreement as well as diagnoses which are apparently difficult to distinguish.

Significance to NINCDS Program and Biomedical Research: This study is a major research endeavor of the NINCDS Pilot Stroke Data Bank Network (Z01 NS 02238-05 OBFS). The consistent application of a diagnostic algorithm for stroke types will enable other research projects utilizing the data bank to investigate stroke type differences and associations with greater precision.

Proposed Course of the Project: The analysis of the data for this project is nearing completion and a manuscript will be prepared for publication.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02502-01 OBFS

PERIOD COVERED October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Medical Studies Database System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI's: Karlin Richardson, Programmer, OBFS, NINCDS
Sylvia Edelstein, Systems Analyst, OBFS, NINCDS

Other: Robert Richter, Mathematician, OBFS, NINCDS
John Michaloski, Jr., Programmer, OBFS, NINCDS
Dr. Jonas Ellenberg, Head, Section on Mathematical Statistics, OBFS, NINCDS
Dr. Young Jack Lee, Mathematical Statistician, OBFS, NINCDS
Selma C. Kunitz, Chief, Computer Applications Section, OBFS, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Section on Computer Aplications

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS: 1.5	PROFESSIONAL: 1.5	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of the Medical Studies Database System (MSDS) is to provide a computerized system that facilitates data handling functions with a high degree of automation that minimizes data collection errors and computer programming. The methodology involves

1) the interactive capture of medical data from data collection forms on to Hewlett Packard 2647A Intelligent Terminal screens which mirror the form and

2) the transfer of the data to a data base management system (DBMS), Hewlett Packard's Image, from which the researcher can abstract information and generate reports from his medical study using English-like query commands. The system operates on a HP-1000 minicomputer under the RTE IVB operating system using IMAGE and Fortran 4X.

Project Description:

Objectives: Provide a computerized system that facilitates the data functions of collection, storage, retrieval and reporting with a high degree of automation that minimizes data collection errors and computer programming.

Methodology: Medical data are captured from data collection forms on to Hewlett-Packard 2647A Intelligent Terminal screens which mirror the form. Data are transferred to a data base management system (DBMS) (Hewlett Packard's DBMS IMAGE) from which the researcher can abstract information and generate reports from his medical study using English-like query commands. The system operates on a HP-1000 minicomputer under the RTE IVB operating system using IMAGE and FORTRAN 4X.

Major Finding: The system is currently undergoing its first trial. The system accomplished its objectives in test data.

Significance to NINCDS Program and Biomedical Research: This system will demonstrate the feasibility of using interactive CRT terminals with menu-like forms to capture medical data; and without programming, the data are converted into a DBMS from which retrieval and reports by researchers are easily made.

Proposed Course of Project: Improved versions of the system will be developed to reduce the number of commands and procedures needed for entry clerks and researchers to accomplish the above data functions.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02496-01 OBFS

PERIOD COVERED October 1, 1980 to September 1, 1981

TITLE OF PROJECT (80 characters or less)

Preliminary Steps for a Data Bank Project in Epilepsy

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.'s Selma C. Kunitz, Chief, CAS, OBFS, NINCDS
Cynthia Gross, Ph.D., Statistician, CAS, OBFS, NINCDS
William Weiss, Chief, OBFS, NINCDS

Other: Nikola Sofijanov, Visiting Scientist, OBFS, NINCDS
W. Allen Hauser, M.D., Neurologist, Sergievsky Institute, N.Y., N.Y.

COOPERATING UNITS (if any)

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

For a data bank to be effective in clinical research, there must be a clear delineation of the research questions that will be addressed. An initial step, then, in proposing a data bank is developing a list of appropriate research questions and hypotheses. A broad set of research questions for a potential data bank in epilepsy has been suggested.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To develop a set of research questions and hypotheses relevant for a data bank in epilepsy.

Methodology: A draft vocabulary has been proposed along with the research design.

Major Findings: This study is in the developmental phase.

Significance to NINCDS Program and Biomedical Research: Epilepsy is a major area of research in NINCDS. A data bank in epilepsy would aid in understanding the clinical course of this disorder.

Proposed Course of Project: This project will provide a basis for ascertaining the feasibility of a data bank network in epilepsy.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02503-01 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Cerebral Palsy Bibliography of Selected References

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Naomi M. Hawkins, Technical Information Specialist, OBFS, OD, NINCDS

Other: Karin B. Nelson, M.D., Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NINCDS

Jonas H. Ellenberg, Ph.D., Chief, Section on Mathematical Statistics, OBFS, OD, NINCDS

COOPERATING UNITS (if any)
Cerebral Palsy and Other Motor Disorders Section, DNB, NINCDS and Section on Mathematical Statistics, OBFS, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20202

TOTAL MANYEARS: .15	PROFESSIONAL: .15	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Preparing a bibliography on cerebral palsy with selected references covering etiology, risk, diagnosis, prognosis, prevalence and incidence and history.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To compile a bibliography of selected references on cerebral palsy, and an updated list of CP References which will be available and useful to investigators doing research on this disorder.

Methodology: Biomedical journals have been scanned for appropriate articles on cerebral palsy, and some of these articles have been stored in files.

The facilities and card catalogs of the NIH Library and the National Library of Medicine (NLM) have been used. NLM's current Medline Files using the computer, and also its backfiles of references from scientific journals have been utilized. The Supplements of Developmental Medicine and Child Neurology have been consulted for selected references on CP.

Major Findings: A bibliography on cerebral palsy is in preparation.

Significance to Biomedical Research and the Program of the Institute: Cerebral Palsy is of interest to the Institute and research on the disorder continues to be done. This reference list will serve as a starting point for researchers who wish to assess the current state of knowledge before beginning a research project.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02404-03 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)
National Survey of Chronic and Debilitating Headache
(Previously titled: "National Headache Survey"

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT
PI: Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBFS, NINCDS
PI: Frederic D. Weinfeld, Ed.D., Chief, Section on Surveys and Demographic Studies, OBFS, NINCDS

COOPERATING UNITS (if any)
The National Center for Health Statistics, The California Medical Clinic for Headache, The Cleveland Clinic, The Diamond Headache Clinic, and The Headache Research Foundation

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION
NINCDS, NIH Bethesda, MD 20205

TOTAL MANYEARS: 1.10	PROFESSIONAL: 1.00	OTHER: .10

CHECK APPROPRIATE BOX(ES)
☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER
☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to design a survey which would measure the prevalence of headache disorders in the United States; to describe the major types of headache by demographic characteristics; to devise a classification system for types of headache, which can be used in epidemiologic studies, using the symptomatology and history reported by patients; to identify the risk factors and other etiological, clinical and environmental factors which may be associated with the occurrence of several major types of headaches; and to determine the impact of headaches on society. Factors such as financial cost, productivity loss, and quality of life will also be assessed.

The survey questionnaire, which includes sections on demography, medical information and history, cost, work and financial loss etc, has been developed. The Feasibility Study has been designed and is now in the data collection stage. Plans for a Pilot Study to validate the questionnaire and to test the methodology are currently being designed.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To identify etiological, clinical, and environmental risk factors which may be associated with the occurrence of several major types of headache; to measure the prevalence of headache disorders in the U.S.; to describe the major types of headache by demographic characteristics; to devise a classification system for types of headache which can be used in epidemiologic studies, using the symptomatology and history reported by patients; and to determine the impact of headaches on society by demographic subgroups of the U.S. population -- factors such as financial cost, work, productivity loss and quality of life will be assessed.

Methodology: The first phase of this project includes the development of a survey questionnaire to collect extensive headache data and the implemention of a small Feasibility Study to test the questionnaire and to develop classifications of headache. The second phase will be a Pilot Study conducted in a defined geographic region during 1982-3. This study will address methodological problems in telephone interviewing and will validate by medical examinations the classification of headache derived from the questionnaire. The final phase will be a large scale National Survey which will be conducted using telephone interviews on a random sample of households.

Significance to NINCDS Programs and Biomedical Research: NINCDS has developed in recent years an extensive interest in headache. Since no national studies of headache have been conducted in the U.S., this epidemiological survey of headache will generate the important national data on headache which has been lacking. The outcomes of this survey will also reveal the socio-economic impact of this most prevalent disorder of our society. Furthermore, the investigation of the association of many potential risk factors with several types of chronic and disabling headaches are expected to produce etiological or therapeutic clues for the management and prevention of headache.

Proposed Course of the Project: The Feasibility Study,the first phase of this project, is now being conducted in collaboration with several headache clinics and the National Center of Health Statistics for the purpose of testing whether reliable headache data can be collected from patients over the telephone using a questionnaire. Patients of these clinics, will be interviewed by telephone to obtain headache history and sociological, demographic and medical information. The reliability of this self-reported data will be investigated by comparison with clinical records. In addition, the utility and the limitations of the operational classification of headache will be evaluated by comparing them with the clinical diagnoses.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02442-02 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)
Feasibility of a National Survey of Speech Defects

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Herbert M. Baum, Ph.D., Demographer, OBFS, NINCDS
PI: Eve Moscicki, Sc.D., Scientist, OBFS, NINCDS
PI: Christy Ludlow, Ph.D., Research Speech Pathologist, CDP, NINCDS

COOPERATING UNITS (if any)
Communicative Disorders Program, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION
NINCDS, NIH Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.10	.00

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

National data on the incidence and prevalence of communicative disorders is scarce. An investigation of the feasibility for gathering such data has been undertaken. One plan is to conduct a survey of both providers and cases. This approach will permit us to also gather data on the cost of the problem, type of services needed, amount of services needed, etc.

Project Description:

Objectives: To estimate the incidence, prevalence, economic cost and severity of various communicative disorders in the population of the United States.

Methodology: The specific methodology will be determined later, but it will include identification and description of cases based on a survey of service providers. A sample of cases thus ascertained will be selected for more detailed investigation.

Major Findings: Since the design of the survey is still being worked on there are no findings to-date.

Significance to NINCDS Program and Biomedical Research: The incidence and prevalence of some communicative disorders, for example, language disorders in children, have not been reliably determined. In addition to collecting data on incidence and prevlance, this survey will attempt to estimate the severity and costs of selected communicative disorders in the population. The availability of this information, collected in a reliable and accurate manner, will aid in planning efforts.

Proposed Course of Project: The conceptual framework for the project is still being constructed. Once this is complete data collection instruments will be designed and a pilot survey conducted. The results of the pilot will determine the feasibility of a nationwide study and assist in the designing of such a study.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02340-04 OBFS

PERIOD COVERED October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Pilot Data Bank Network Project in Coma

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Selma C. Kunitz, Chief, Computer Applications Section, OBFS, OD, NINCDS
Other: James M. Dambrosia, Ph.D., Mathematical Statistician, SMS, OBFS, NINCDS
Cynthia Gross, Ph.D., Biostatistician, CAS, OBFS, NINCDS
Irene Fishman, M.A., Statistician, CAS, OBFS, NINCDS
Sylvia Edelstein, Systems Analyst, CAS, OBFS, NINCDS
Barbara Nichols, Programmer, CAS, OD, NINCDS
Dr. Lawrence Marshall, University Hospital at San Diego, CA
Dr. Howard Eisenberg, University of Texas Medical Branch at Galveston, TX
Dr. John Jane, Univ. of Virginia, Charlottesville, VA.
Dr. Donald Becker, Medical College of Virginia, Richmond, VA.
Dr. Robert Grossman, Baylor University, Houston, Texas
Dr. Kamran Tabaddor, Albert Einstein Medical College, Bronx, NY

COOPERATING UNITS (if any) University Hospital at San Diego, CA; University of Texas Medical Branch at Galveston, Texas; University of Virginia Medical Center, Charlottesville, VA Medical College of Virginia, Richmond, VA, Albert Einstein School of Medicine, Bronx, N.Y.; Baylor School of Medicine, Houston, TX.

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 2.5	PROFESSIONAL: 2.0	OTHER: .5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A Pilot Traumatic Coma Data Bank Project has been implemented with the objectives of developing common data collection methods and a uniform clinical vocabulary to insure inter-center comparability for the collection of accurate data for multicenter studies of severe head injuries. This is a demonstration project intended to provide guidelines and protocols for expansion to additional centers and other neurological disorders. The data collection in the pilot has focused on refinement of measures of outcome following head trauma, comparing primary brain injury characteristics (accident details, injury types and location) with outcome, and exploring the impact of secondary insults to the brain (shock,hypoxia, elevated ICP) on outcome.

Project No. Z01 NS 02340-04 OBFS

Project Description:

Objectives: The primary objective of this project is to develop an interactive data bank network for traumatic coma patients. This data bank will be used for clinical research and patient management.

Methodology: This is a multicenter study of severely head injured persons, their study elibility determined by a Glasgow Coma Score of 8 or less and a traumatic, non-penetrating source of injury. Data bank teams of neurosurgeons, nurses and technicians located at six hospital centers geographically dispersed throughout the United States are utilizing the same data collection forms and procedures and are entering data into a central data bank. A wide variety of data editing and quality control methods are used in this study. The information collected includes demographic data, accident details, injury details, clinical course and outcome. Sources of data include the patient, family and hospital records. Data are retrieved from the central data bank and analyzed by center or subgroup. Statisticians at OBFS, in collaboration with the local clinical data bank researchers, are performing the data analyses.

Major Finding: This data bank has refined and is utilizing a uniform clinical vocabulary to collect patient data, including symptoms, test results, therapies and outcomes. The Glasgow Coma Scale is part of this vocabulary. Over 250 severely head injured patients were accrued as of June 1981 and data collection is continuing.

Significance to the NINCDS Program and Biomedical Research: The Traumatic Coma Data Bank is important for several reasons. This data bank will provide a large body of high quality data for clinical research on the factors influencing survival and quality of life following coma. In addition, the data bank will serve as an efficient mechanism for collecting, storing, and retrieving the information collected on a single patient and groups of patients. The number of therapies and monitoring devices commonly utilized during the acute phase of managing traumatic coma necessitates a highly organized data handling capacity.

Proposed Course of the Project: This is a three-year collaborative pilot project involving six centers which collect patient data, a Data-Bank Maintenance Center, and OBFS staff which provides systems analysis and has the responsibility for data analysis. During the first stage of its operation the effort was focused on refining the uniform vocabulary and developing data collection methods. The second stage was a test phase when this vocabulary and procedures for collection, entry and retrieval were implemented on a trial basis. Currently data are being collected and entered, subject to a wide variety of data quality enhancement efforts. Preliminary analyses of the data collected in the first year are being performed and plans for final recommendations for a main phase are being formulated.

Publications: "A National Traumatic Coma Data Bank" Proceedings of the Fourth Annual Symposium of Computer Applications in Medical Care: Editor Joseph T. O'Neill, Vol. 2, 1333-1339, November, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02238-05 OBFS

PERIOD COVERED October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Pilot Data Bank Project Network in Stroke

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Selma C. Kunitz, Head, Computer Applications Section, OBFS OD, NINCDS

Other: Cynthia Gross, Ph.D., Biostatistician, CAS, OBFS, NINCDS
Barbara Nichols, Programmer, CAS, OBFS NINCDS
Sylvia Edelstein, Systems Analyst, CAS, OBFS, NINCDS
James Dambrosia, Ph.D., Mathematical Statistician, SMS, OBFS, NINCDS
Irene Fishman, M.A., Statistician, CAS, OBFS, NINCDS
Dr. Albert Heyman, Duke University Medical Center
Dr. Jay Mohr, University of South Alabama College of Medicine
Dr. Thomas Price, University of Maryland School of Medicine
Dr. Philip Wolf, Boston University Medical Center, School of Medicine

COOPERATING UNITS (if any)
Duke University Medical Center, Durham, NC; Univ. of Maryland School of Medicine, Baltimore, MD; University of South Alabama, College of Medicine, Mobile, Ala.; Boston University Medical Center, Boston, MA

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.5	2.0	.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objectives of the Pilot Stroke Data Bank are: a.) to develop a uniform method of data collection utilizing standard clinical nomenclature and data collection methods to obtain patient histories, diagnosis, treatment and outcome data in the course of routine care; b.) to implement an interactive data bank network enabling the pooling of clinical data among institutions for collaborative inter-institutional studies and to provide rapid access to large quantities of clinical data; and c.) to demonstrate the feasibiity of such a network, including the computer aspects, the collaboration among a number of institutions, to serve as a model for neurological diseases and disorders. This project has met its immediate objectives and has been approved to proceed to a main phase. Currently the collected data on over 1000 stroke patients are being analyzed for studies of stroke course and diagnosis.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: The primary objective of this project is to develop a computerized interactive data bank network which will contain uniform, longitudinal data on stroke patients to aid both research and patient management. This is a collaborative project involving four separate medical centers which collect data, a Data Bank Maintenance Center to store and manipulate the data and staff at OBFS who have the responsibility for project direction, systems analysis, and data analysis. This project has met its objectives and will continue into a full phase with competitive awards.

Methodology: This is a multicenter study of stroke patients, excluding persons under 20 years of age and strokes due to brain tumor or trauma. Data bank teams at four clinical centers in the United States have, using the same forms and procedures during the Pilot, collected data on approximately 1,000 stroke patients. These data include demographic information, medical history, stroke course and outcome. Patients have been followed up to two years. All data are entered into a central data bank and retrieved for data analysis by statisticians at OBFS in collaboration with the neurologists at the Clinical Centers.

Major Findings: This project has produced a uniform vocabulary of data elements including test results, medical and surgical therapy, complications, and measures measures of stroke deficit and recovery, and has collected data on approximately 1,000 stroke patients from the collaborating centers. It has also produced a diagnostic algorithm for stroke which is described in the summary.

Significance to the NINCDS Program and Biomedical Research: The Pilot Data Bank Network in Stroke has demonstrated the feasibility and utility of having medical centers collaborate to provide a resource of high quality data on the clinical course of stroke. This project will serve as a prototype for a national data bank network for other neurological disorders.

Proposed Course of the Project: The Pilot Stroke Data Bank Network is in the third and final year of its pilot phase. Data are being collected, examined for errors, and added to each data base. A "clean-up" phase will begin in August when all new patient acquisition will cease and the data collection will be focused on verifying follow-up status of surviving data bank patients, obtaining death information where necessary, and correcting any omissions or errors which have been identified. Manuscripts describing the data bank and its findings are in progress for publication.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02341-04 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)
Type-Specific Stroke Mortality Trends
(Previously entitled: "Stroke Mortality Study")

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Herbert M. Baum, Ph.D., Demographer, OBFS, NINCDS
PI: Murray Goldstein, D.O., Acting Director, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION
NINCDS, NIH Bethesda, MD 20205

TOTAL MANYEARS: .30	PROFESSIONAL: .20	OTHER: .10

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The investigators used the NCHS mortality data tapes for 1968-1976 to examine age-type-specific stroke mortality trends by race, sex, and hypertension status. There are many problems inherent in arriving at conclusions in a study based on death certificates, but the study explores the shortcomings of the data to arrive at implications. A general decline in stroke death rates was observed with the largest declines being observed for hemorrhagic strokes and for nonwhites. An examination of the data by hypertension status indicates the need for clinical studies which will examine the relationship between hypertension and stroke mortality.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To determine whether the observed decrease in stroke mortality also would be present in the various diagnostic subcategories. Limitations in the subcategories to be data permitted only the following examined: hemorrhages, infarctions, and "poorly-addition, defined." In hypertension status, as reported on the death certificate, was purpose was to examined. The examine the relationship between hypertension and stroke mortality.

Methodology: Computer tapes, issued by the National Center for Health Statistics, containing all death certificates in the United States for the period 1968-1977 were used. All certificates where stroke (ICDA-8 Codes 430-438) was coded as the underlying cause of death were selected for study. The data were then tabulated by age, race, sex, type of stroke, and hypertension status. Using data from the U.S. Census and the National Health and Nutrition Examination Survey, age-specific or age-adjusted rates were calculated, and then the trends for the period were examined. The percentage change was used as the mechanism for quantifying the observed trend.

Major Findings: For each of the three diagnostic categories of stroke, there was a decline in the mortality rates over the study period; however, the percentage change was not the same for the various categories. The largest percentage decline was observed for hemorrhagic strokes. The data indicate that either the reporting of hypertension status on the death certificates has a major error in it or that once a stroke has occurred that death rates are lower for those with mention of hypertension. The study did not arrive at a definitive conclusion but noted that a detailed clinical study is needed to investigate this finding.

Significance to NINCDS Program and Biomedical Research: Much of the nation's effort with respect to reducing stroke mortality has been channeled into hypertension control. The reduction in stroke mortality rates preceded the inception of the hypertension control program. This study has indicated that there are other relevant factors which need to be identified and that more research in the area is needed.

Proposed Course of Project: A paper was presented at the First International Syposium on Brain Heart Relationships in Jerusalem. An article has been writted and submitted for publication. Once accepted for publication the project will terminate.

Publications: None.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02403-03 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)
The Incidence and Prevalence of Stroke

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Herbert M. Baum, Ph.D., Demographer, OBFS, NINCDS
PI: Frederic D. Weinfeld, Ed.D, Chief, Surveys and Demographic Studies Section, OBFS, NINCDS

COOPERATING UNITS (if any)
Morton Robins, Project Director, Nationwide Study of Stroke, Westat Inc. Rockville, Maryland

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION
NINCDS, NIH Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.25	.15	.10

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Estimates of the incidence and prevalence of stroke were generated from the findings of the National Study of Stroke. The estimates were compared with other commonly accepted estimates. The results have been published as a chapter in the monograph: The National Survey of Stroke.

The project is now completed.

PHS-6040
(Rev. 2-81)

Project Description

Objectives: To generate estimates of the incidence and prevalence of stroke using data gathered from the Nationwide Study of Stroke. Also, to compare the results with those of other studies.

Methodology: The Nationwide Study of Stroke is a national probability sample of hospitalized stroke victims. An algorithm was used to determine whether a given case met the study criteria of having a stroke. The hospital record was abstracted to obtain the necessary information. A survival approach, using life table survival rates, was used to estimate the prevalence population as of July 1, 1976.

Major Findings: The incidence of hospitalized acute stroke is 297,000 yielding a rate of 14.7 per 100,000 population for the period 1975-1976. The age-specific incidence rates escalate rapidly with advancing age. Also, the age-specific incidence rates for men are higher than those for women among persons 35 years and older. The standardized incidence ratio for men is 44 % higher than that for women. Prevalence is estimated to be 1.7 million, yielding a rate of 743 per 100,000 on July 1, 1976. The largest number of prevalence cases are in the 55-64 age group.

Significance to NINCDS Program and Biomedical Research: The National Survey of Stroke was undertaken to fill the void with respect to reliable national data on stroke The results of this Survey will be used by the Institute and heath planners to justify program and budgetary requests.

Proposed Course of Project: Project is now completed.

Publications:

Baum, H.M. and Robins, M. "Chapter 5: Survival and Prevalence" in Weinfeld, F.D. (ed.) The National Survey of Stroke. Stroke 12 (Part II): I-59 - I-68, 1981.

Robins M. and Baum H.M. "Chapter 4: Incidence" in Weinfeld F.D. (ed.) The National Survey of Stroke. Stroke 12 (Part II): I-45 - I-68, 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02405-03 OBFS

PERIOD COVERED

October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Assessment of Strategies for Analyzing Data from Small Area Health Surveys (Previously titled: "Assessment of Strategies for Analyzing Data from Small Area Mortality Surveys"

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Dallas W. Anderson, Ph.D., Survey Statistician, OBFS, OD, NINCDS

COOPERATING UNITS (if any)

W. Edwards Deming, Ph.D., Consultant in Statistical Studies, Washington, D.C.

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.09	.01

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Studies of small areas, such as communities or counties, are an important tool of epidemiologists, who are interested in studying distributions of diseases in populations. Many studies of this type have been reported in the scientific literature. An assessment of techniques of analysis frequently used in these studies was initiated to determine their adequacy for use in the NINCDS survey of major neurological disorders in Copiah County, Mississippi (Y01-NS-70031, N01-NS-7-2357).

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: The purpose of this investigation is to explore the implications for data analysis in small-area (or community) surveys when a descriptive point of view is taken and when an analytic point of view is taken. A by-product of this investigation will be a comparison of what can be learned from small-area surveys (that rely upon judgment sampling) and from large-scale national surveys (that rely upon probability sampling).

Methodology: Pertinent, statistical methods found in scientific literature ill be reviewed.

Major Findings: These will be reported in a paper to be published in an appropriate journal.

Significance to NINCDS Program and Biomedical Research: Small-area health surveys continue to be an important tool in epidemiologic work at NINCDS and elsewhere. This work will lead to a better understanding of the uses and limitations of findings from these surveys.

Proposed Course of Project: Following a review of the scientific literature, the investigators will summarize the findings of the inquiry in a manuscript that will be submitted for publication to an appropriate journal.

Publications: None.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02406-03 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)
The Frequency of Neurological Disorders Among Hospital Discharges

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT
PI: Herbert M. Baum, Ph.D., Demographer, OBFS, NINCDS

COOPERATING UNITS (if any)
Dr. Donald Smith, Hospital Care Statistics Branch, NCHS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION
NINCDS, NIH Bethesda, MD 20205

TOTAL MANYEARS: .05	PROFESSIONAL: .05	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Hospital Care Statistics Branch has agreed to provide us with data on hospital discharges where a neurological disorder is indicated. A list of ICDA codes has been prepared for conditions of primary interest to the Institute. By examining the data on the first discharge diagnosis and on all listed discharge diagnoses we will monitor the secular trends. In addition, by constantly updating the data, we intend to be able to handle requests for data on hospitalization of neurological conditions. This will become an annual reporting effort.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To provide the NINCDS Program Directors with baseline data which could be used for program planning and budget justifications.

Methodology: A list of disorders, of interest to the staff of the Institute, was compiled and converted into ICDA - 8 codes. This was then forwarded to the National Center for Health Statistics where the number of discharges with the given code were tabulated. The tabulations were done by first listed diagnosis and all listed diagnoses. A comparison with all codes and the neurologic data for previous years are made.

Major Findings: There were no major findings during this fiscal year because we have been unable to convert the codes into the 9th ICD.

Significance to NINCDS Program and Biomedical Research: The absence of reliable data on the incidence and prevalence of most neurologic disorders has hampered planning efforts. The Hospital Discharge Survey provides one way to allieviate this need.

Proposed Course of the Project: An attempt will be made to prepare a list of ICD - 9 codes for the National Center for Health Statistics. Then, based upon this list the number of discharges could be tabulated.

Publications: None.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02237-05 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)
Development and Design of a Pilot Study for a National Survey of Epilepsy

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Dallas W. Anderson, Ph.D., Survey Statistician, OBFS, NINCDS
Frederic D. Weinfeld, Ed.D., Chief, Section on Surveys and Demographic Studies, OBFS, OD, NINCDS

COOPERATING UNITS (if any)
W. Allen Hauser, Sergievsky Center, Columbia University, New York, New York
Joseph Steinberg, Survey Design, Inc., Silver Spring, Maryland

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.00	.00	.00

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This work was undertaken to develop a broad strategy for collecting morbidity data on epilepsy. The sources of the data would include: pharmacies, physicians, and epileptics. This broad strategy was incorporated into a Request for Proposal and provided bidders with a framework on which to construct a design for a pilot survey. A contract (N01-NS-8-2383) for doing the pilot survey was subsequently awarded to Research Triangle Institute of North Carolina. This project is now completed.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: This investigation was the background research necessary for drafting a Request for Proposal (RFP) pertaining to a pilot study for a National Survey of Epilepsy. The purpose of the pilot study was to develop and test the methodology for collecting data from pharmacies, physicians, and epileptics.

Methodology: Survey techniques, statistical methods, and pharmacy practices were reviewed, and a design for the survey was prepared.

Major Findings: The survey design was incorporated into an RFP, providing a framework for a design of a pilot study.

Significance to NINCDS Program and Biomedical Research: The study of epilepsy is a major component of the NINCDS program. Although epilepsy is one of the more common neurological disorders, it occurs rarely in the general population and is sometimes hidden from view because of social stigma. The rarity and the social stigma combine to form a great obstacle to those who want to find out about the magnitude of the disorder in the U. S. population. This investigation is the first in a series of studies to find methodology that can be used to overcome that great obstacle.

Proposed Course of Project: The objective of this project has been reached. The project is completed.

Publications: None.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02239-05 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)
Design of Health Interview Survey Questionnaire Supplements
(formerly Design of Convulsive Disorder Questionnaires)

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Frederic D. Weinfeld, Chief, Surveys and Demographic Studies Section, OBFS, NINCDS

PI: Dallas W. Anderson, Ph.D., Survey Statistician, OBFS, OD, NINCDS

COOPERATING UNITS (if any)
Clint Burnham, Health Interview Survey, NCHS
W. Allen Hauser, M.D., St. Paul-Ramsey Hospital, St. Paul, Minn.
Lee Kudrow, M.D., California Medical Clinic for Headache

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION
NINCDS, NIH Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.10	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project involves the design and field testing of questionnaires to be used as supplements to the NCHS's Health Interview Survey (HIS). The first such questionnaire was designed to collect information on the number of persons who had had a stroke, diagnosed or undiagnosed, and their hospitalizations. This questionnaire was included in the 1977 HIS.

Questionnaires are being designed as supplemental modules for the HIS. One questionnaire will collect information on those persons with convulsive disorders. Another questionnaire will collect information on headache. The data collected will be used to provide national estimates of the prevalence of these disorders.

Project Description:

Objectives: The primary purpose of this project is to develop sets of questions, or modules, for selected neurologic disorders which can be added as supplements to the Health Interview Survey (HIS) which is conducted each year by NCHS. The data collected will be used to provide national estimates of the prevalence of these disorders. The prevalence population will be described using the demographic and medical information in the HIS.

Methodology: The HIS is an annual survey which has been conducted over the past 20 years using a national probability sample of some 40,000 households. Personal interviews are conducted with one family member who responds for all the household members. The interviews are conducted using a very extensive questionnaire covering the health and medical history of the family members. Every year supplements for specific health conditions are added to the core questionnaire.

The data collected by the HIS supplements will be analyzed and will provide national estimates of the prevalence of convulsive disorders and headaches. The national data from the complete HIS will provide, by cross-tabulation, descriptions of the prevalence population by demographic subgroups.

Major Findings: Findings from the first HIS supplement of stroke have been published by NCHS and an article prepared by OBFS will be published early next year. Future findings will also be submitted to appropriate journals and publications.

Significance to NINCDS Program and Biomedical Research: National estimates of the prevalence of selected neurologic disorders will help fill the need for reliable national data on convulsive disorders and for headache. The prevalence data and the descriptions of the prevalence population will be valuable to epidemiologists. The data will also be useful to the Institute in program planning.

Proposed Course of Project: A screening questionnaire on epilepsy and convulsive disorders was administered in the survey of major neurologic disorders conducted in Copiah County, Mississipppi (N01-NS-7-2357). This questionnaire will be refined after the analyses of the neurologic examinations are completed. Another module of questions on headache is being developed in cooperation with researchers in headache clinics. The completed modules will be submitted to NCHS for inclusion in future HIS surveys.

Publications:

Moss, A.J. "Stroke Survivors Among the Noninstitutionalized Population 20 Years of Age and Over: United States, 1977." Advance Data 68: 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02494-01 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)
The Prevalence of Multiple Sclerosis in Colorado

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT
PI: Herbert M. Baum, Ph.D., Demographer, OBFS, NINCDS

COOPERATING UNITS (if any)
Drs. D. Thompson and J. Burks, Rocky Mountain M.S. Center, Denver

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION
NINCDS, NIH Bethesda, MD 20205

TOTAL MANYEARS: .05	PROFESSIONAL: .05	OTHER:

CHECK APPROPRIATE BOX(ES)
☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Rocky Mountain Multiple Sclerosis Center is the only center of its type in the State of Colorado. Using the records from the center, and the Multiple Sclerosis Chapters we will estimate the prevalence of the disease in Denver and the State. If this effort is successful additional collaborative efforts will be undertaken.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To determine the incidence and prevalence of multiple sclerosis in the Denver area and possibly the State of Colorado. Using these data as a base, comparisons will be made with the data from the Rocky Mountain M.S. Center to ascertain what biases may be present in the clinic population.

Methodology: A number of patient lists for Denver and Colorado are available. What is unknown is the completeness of each list. A mail survey of physicians and hospitals will be used to identify all the multiple sclerosis patients in a given area. The results from that survey will be matched to responses from a survey of known or suspected cases as identified by the M.S. Center, the local M.S. Organization, and the regional chapter of the National M.S. Society. Measures of completeness can then be calculated as well as estimates of the incidence and prevalence of the disease

Major Findings: The study is being organized and there are therefore no findings to date.

Significance to NINCDS Program and Biomedical Research: There is a great need for descriptive and clinical studies of M.S. patients. This study, in addition to ascertaining the incidence and prevalence, will help identify any biases in the current patient population of the Rocky Mountain M.S. Center. Once the biases are ascertained the clinic population will be used for descriptive and clinical studies.

Proposed Course of Project: The design of the survey instruments is underway. Once all the necessary data elements are defined and a data collection form constructed the survey will begin. The staff of the M.S. Center will be responsible for the field work and editing of forms. The data will then be computerized and analyzed.

Publications: None.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02495-01 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)
Analysis of Data From the National Survey of Multiple Sclerosis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Herbert M. Baum, Ph.D. Demographer, OBFS, NINCDS
Karlin Richardson, Programmer, OBFS, NINCDS

COOPERATING UNITS (if any)
Beth Rothschild, National Analysts; Drs. Sheinberg, La Rocca, and Kornblith, Albert Einstein College of Medicine, Yeshiva University

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION
NINCDS, NIH Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.30	.25	.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The National Survey of Multiple Sclerosis (NSMS) is a probability sample of all multiple sclerosis patients in the conterminous United States. The Survey gathered detailed data on the disease, employment, and social history of over 1200 cases. The Office of Biometry and Field Studies in conjunction with other researchers in the field of multiple sclerosis is undertaking a detailed analysis of these data. It is hoped that some concept of how disease factors affect the lives of these individuals will be obtained.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To prepare a series of articles on the incidence and prevalence of multiple sclerosis in the United States and to describe the prevalence population in terms of disease, employment, and social history. Of primary importance is how this disease has affected the individual and the family.

Methodology: The data from the National Multiple Sclerosis Survey (NMSS) is the source for the information. The NMSS was a two-stage probability sample involving health care practioners and patients. The data were gathered from 1240 patients, representing a weighted probability sample of all M.S. patients. The individuals were given face-to-face interviews. They submitted cost diaries for the 90 day period following the interview, and shortly thereafter a telephone interview was administered.

Major Findings: A journal article on the incidence and prevalence of the disease is now in press.

Significance to NINCDS Program and Biomedical Research: The National Multiple Sclerosis Commision Report has cited the lack of accurate national statistics which are needed. This survey was initiated to fill that gap.

Proposed Course of Project: Work is progressing on the psycho-social aspects of M.S. In conjunction with that effort work will begin on the symptomatology and functional status of the patients.

Publications: None.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02444-02 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)
Statistical coordinating center for the phenobarbital clinical study ** (previously titled "Cognitive and Behavioral Effects of Phenobarbital in Young Children").

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Young Jack Lee, Mathematical Statistician, Section on Mathematical Statistics, OBFS, NINCDS

Others: Jonas H. Ellenberg, Chief; Martha Griswold, Statistician; Section on Mathematical Statistics, OBFS, NINCDS
Karin B. Nelson, Chief; Deborah G. Hirtz, Expert Consultant; Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS
Sylvia Edelstein, Systems Analyst; Karlin Richardson, Programmer; Section on Computer Applications, OBFS, NINCDS

COOPERATING UNITS (if any)
Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies, OD

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS: .30	PROFESSIONAL: .20	OTHER: .10

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Statistical design considerations for the study were developed for the RFP, as well as the functions and organization of the statistical coordinating center.

During this fiscal year, precoded data forms, and computer systems for data entry and management are being developed in collaboration with the Computer Applications Section. The system will handle patient status and data tracking, data quality assurance, and production of simple charts and tables. Edited data will be transferred to the DCRT, NIH Computer for statistical analyses.

**[This study is in support of the DNB/NDP/NINCDS contract study entitled: "Behavioral and Cognitive Side Effects of Phenobarbital Used for Prevention of Febrile Seizure Recurrence." The project officer will be Dr. Karin B. Nelson, DNB, NDP, NINCDS. The contract is in the final negotiation stage.]

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: The Office of Biometry and Field Studies is collaborating with DNB, NDP in the clinical study evaluating the effect of the long-term phenobarbital treatment on cognitive functions and behavior of febrile seizure children. The OBFS is the Statistical Coordinating Center for the study.

Methodology: The Statistical Coordinating Center is composed of the Operations Office, Computer Center and Statistics Office. The Operations Office is staffed jointly by DNB, NDP and OBFS, and the Computer Center and Statistics Office by OBFS alone.

Major Findings: This project is in progress.

Significance to NINCDS Program and Biomedical Research: Better quality control of data, constant monitoring of the study progress, and better interactions among project directors, clinical investigators, computer programmers, and statisticians will be possible. The OBFS and DNB, NDP scientists will gain a valuable experience from coordinating this clinical trial. As the data will be managed by the OBFS, the program area scientists can concentrate on the scientific aspects of the project.

Proposed Course of Work: This is a continuing project which will go on into 1986.

Publications: None.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02445-02 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)
A Phase II Clinical Trial of Lisuride versus Bromocriptine (previously titled "A Clinical Trial of Bromocriptine and Lisuride for the Treatment of Parkinson Disease").

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. J.M. Dambrosia, Mathematical Statistician, OBFS, NINCDS
P.I. P. Le Witt, Experimental Therapeutics Branch, IRP, NINCDS
P.I. D.B. Calne, Head, Experimental Therapeutics Branch, IRP, NINCDS
P.I. J. Sanes, Laboratory of Neuropsychology, NIMH

COOPERATING UNITS (if any)
Experimental Therapeutics Branch, IRP, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.4	.3	.1

CHECK APPROPRIATE BOX(ES)
☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER
☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study compares the effectiveness of Lisuride versus Bromocriptine in a randomized, double-blind, two-period, crossover clinical trial. Patient responses to treatment are measured clinically using a modified Columbia rating scale and objectively by computerized sensing equipment. Adverse drug effects are monitored throughout the trial. The report of this trial has been accepted by Neurology. This project is now completed.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: Determination of the relative effectiveness of Lisuride versus Bromocriptine in the treatment of Parkinson disease. The study also provides a basis for comparison of adverse effects in relationship to dose levels of the drugs.

Methodology: A randomized, double-blind, two-period crossover design is employed to compare responses from the two drugs. Study period effect and treatment by period interaction effect are tested in an analysis of variance split plot model. Conditional direct treatment effects are tested in the absence of period and interaction effects, or on the first period responses only if interactions are present. Adverse effects are monitored throughout the study.

Major findings: The only difference to emerge between the two drugs was slightly better control of akinesia with Bromocriptine. Those patients taking high doses of Bromocriptine tended to also take high doses of Lisuride. Similar adverse effects were noted for both drugs.

Significance to NINCDS Program and Biomedical Research: The study provided an evaluation of relative effectiveness of Lisuride and Bromocriptine at higher dose levels of Lisuride than were used previously. Groundwork for a detailed study of the pharmacokinetics of Lisuride was established, as was information regarding Lisuride dose-response.

Proposed Course: Based on information obtained from the clinical trial, a Phase II clinical trial of Bromocriptine versus Pergolide will be initiated. Further studies of the pharmacokinetics of Lisuride are planned for the future.

Publications:

"Lisuride and Bromocriptine Treatment in Parkinson Disease: A Double-Blind Study," accepted for publication by *Neurology*, 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02411-03 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)
Survey of Practice in the Management of Febrile Seizures (previously titled "Survey of Management of Children with Febrile Seizures").

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Young Jack Lee, Mathematical Statistician, Section on Mathematical Statistics, OBFS, NINCDS
P.I. Jonas H. Ellenberg, Chief, Section on Mathematical Statistics, OBFS, NINCDS
P.I. Deborah G. Hirtz, Pediatric Neurologist, Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS
P.I. Karin B. Nelson, Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS

COOPERATING UNITS (if any)

Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.15	.15	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A survey of clinical practice in the management of febrile seizures is ongoing. The survey form is to be submitted for OMB clearance. The survey of approximately 10,000 physicians in various specialities will determine which medical discipline(s) treat most children with febrile seizures, what criteria physicians use to determine therapy, the regimens prescribed and the specific goals of therapy.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To ascertain the clinical determinants and rationale used in deciding how to manage children with febrile seizures. To ascertain the medications, doses and methods of administration of recommended prophylaxis.

Methodology: Sampling frame will be composed of neurologists, child neurologists, pediatricians and general/family practioners. The sample size of 10,000 will be randomly selected from the American Medical Association list of practicing physicians. The data entry, management and analysis will be done by the OBFS staff.

Major Findings: NA

Significance to NINCDS Programs and Biomedical Research: In addition to questions of cost, feasibility, purpose etc. in regard to the implementation of a clinical trial on the use of chronic prophylaxis in children with febrile seizures, the question of its impact on the practice of medicine has been repeatedly raised. In this regard, it is important to know which if any drugs are currently being used and in what way they are being administered. It is argued that a proclamation by a select group of experts as to what regimen is now in use or increasing in population, the drug dosage, and methods of administration may not represent the actual practice of medicine. If we establish a protocol which is not in line with physician's practice or outlook, then after a protracted and expensive trial the results may be ignored. A survey is under way of current practice and of clinical determinants and rationale for management of children with febrile seizures, geographic area, where and when trained, and type of practice. This will be used as an element in considering the need for and potential impact of further clinical investigations.

Proposed Course of Work: Following OMB clearance, the survey form will be printed and mailed out. At least one followup mailing is anticipated.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02446-02 OBFS

PERIOD COVERED October 1, 1980, through September 30, 1981

TITLE OF PROJECT (80 characters or less)

** Parkinson's Disease in Twins previously titled "Parkinson Twin Studies".

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. R. Eldridge, Section on Neuroepidemiology, IRP, NINCDS
P.I. C. Ward, Experimental Therapeutics Branch, IRP, NINCDS
P.I. J. Dambrosia, Mathematical Statistics, OBFS, NINCDS

COOPERATING UNITS (if any)

Experimental Therapeutics Branch, IRP
Section on Neuroepidemiology, IRP

LAB/BRANCH
Office of Biometry and Field Studies, OD

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.20	.15	.05

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Twin pairs, discordant with respect to Parkinson's disease, are evaluated for zygosity and the presence of Parkinson disease. Clinical, laboratory, historical, and psychometric data are obtained for both the pro-band and the co-twin. Statistical analysis of these matched pairs will attempt to identify risk factors and examine differences between the pro-bands and co-twins.

**[This study is the OBFS/NINCDS portion of a larger study entitled; Genetic Epidemiology Studies in Multiple Sclerosis and Other Multifactorial Neurologic Disorders (Z01 NS 02167-06 ODIR). The principal investigator on the overall study is Dr. Roswell Eldridge, NES, ODIR, IRP, NINCDS.]

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: This study attempts to describe the etiology of Parkinson's disease in a cohort of twins discordant with respect to Parkinson's disease. Psychometric functions, zygosity, medical history and current medical status data provide a basis for tracking differences between the pro-bands and the co-twins.

Methodology: Most analyses of pro-band-co-twin differences are based on the usual methods of matched pairs. Use of profile analysis provides summary measures of differences for psychometric functions. Graphic and descriptive statistical methods are used to present the difference data.

Major Findings: The study is in progress.

Significance to NINCDS and Biomedical Research: This study will provide valuable information on the etiology of Parkinson disease, thus establishing a basis from which epidemiological studies can be planned in the future. Psychometric aspects of the study address questions concerning the early psychological behavior of Parkinson's patients and behavioral changes that occur after Parkinson's symptoms.

Proposed Course: The data collection phase of the study will be completed in October, 1981. Analysis of the data and report writing will continue through 1982.

Publications: None.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02414-03 OBFS

PERIOD COVERED
October 1, 1980, through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Early Stopping Rules Used in Clinical Trials previously titled "Simulation of Early Stopping Rules Used in Clinical Trials".

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. James Dambrosia, Mathematical Statistician, Section on Mathematical Statistics, OBFS, NINCDS
P.I. Jonas H. Ellenberg, Chief, Section on Mathematical Statistics, OBFS, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.1	.1	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project assesses the various techniques proposed for early stopping of clinical trials in the face of unexpected evidence of the failure or success of a particular regimen, prior to the scheduled termination of a trial.

Distribution theory for these procedures is either mathematically intractable or only known asymptotically. A computer simulation study for comparison of the various procedures is being considered.

OBFS organized an invited paper session at the Spring 1981 Biometrics meeting concerning this topic. It is expected that the papers from this session will be published together.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To assess the various techniques proposed for early stopping of clinical trials in the face of unexpected evidence of the failure or success of a particular regimen, prior to the scheduled termination of a trial.

Methodology: The OBFS organized an invited paper session at the Spring 1981 Biometrics meeting concerning this topic. The session stressed both the theoretical and practical aspects of early stopping of clinical trials. In addition, the possibility of assessment of the various statistical procedures proposed for guidance in early trial termination is being investigated. Distribution theory for these procedures is either mathematically intractable or only known asymptotically and it is likely we will need to resort to simulation studies.

Significance to NINCDS Program and Biomedical Research: The Institute is actively involved in clinical trial activity and the question of early stopping can be an important issue in the implementation of any trial. These results will help in the clinical trial monitoring committee in its decision process for any potential early stopping of resolutions.

Proposed Course of Contract: The papers from the Biometrics Session are expected to be published. Due to staffing limitations, no work in FY'82 is expected on the simulation studies evaluating the early stopping procedure.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02421-03 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Assessment of Robustness of Missing Data Techniques

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Jonas H. Ellenberg, Chief, Section on Mathematical Statistics, OBFS, NINCDS

Other: Karen Keating, Statistician, Section on Mathematical Statistics, OBFS, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS: .3	PROFESSIONAL: 0	OTHER: .3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Several techniques for handling missing observations in the statistical analysis of large data sets have been proposed. All of the existing techniques require certain assumptions about the underlying model; generally these include the assumption that the missing data are randomly generated and randomly dispersed within the data set. This project is assessing the robustness of the standard techniques to variations in the underlying assumptions, such as nonrandomness and high intercorrelations within the data set. The project will be accomplished using computer simulation on our HP-1000 minicomputer. No further work is expected on this project.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: Several techniques for handling missing observations in the statistical analysis of large data sets have been proposed. All of the existing techniques require certain assumptions about the underlying model; generally these include the assumptions that the missing data are randomly generated and randomly dispersed within the data set. The objective of the project is to assess the robustness of the standard techniques to variations in the underlying assumptions, such as randomness and high intercorrelations within the data set.

Methodology: Since a theoretical or mathematical approach appears to be intractible, without extensive simplifying assumptions, computer simulation was chosen as the mechanism for analysis. This approach allows for a wide range of perturbations to be applied to the assumed model with little or no simplification in the underlying model, which might limit the generalizability of the results.

Major Findings: The work on this project is in progress.

Significance to the NINCDS Program and Biomedical Research: The development of selection criteria for missing data techniques to be used in large data sets can be directly applied to the analysis of the NINCDS Collaborative Perinatal Project, a large scale prospective study involving 60,000 pregnant women and the followup of their children to 7 years of age. The results can also be applied to other large scale data sets.

Proposed Course of Contract: Due to limitations of staff availability, no further work is expected on this project in the next fiscal year.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02412-03 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Consensus Meeting on the Management of Children with Febrile Seizures

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Jonas H. Ellenberg, Chief, Section on Mathematical Statistics, OBFS, OD, NINCDS
P.I.: Karin B. Nelson, Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS

COOPERATING UNITS (if any)

Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.35	.3	.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A consensus meeting on the management of children with febrile seizures was held in May, 1980, in an effort to reach general agreement on the risks of sequelae in children with febrile seizures and compare them with the potential risks and benefits of prophylaxis with anticonvulsants. The consensus statement concluded that the prognosis for children with febrile seizures was excellent and that there is no evidence that prophylaxis can prevent long-term sequelae. It excluded some 60% of all children with febrile seizures from any consideration of treatment. During the current fiscal year, a monograph derived from the consensus meeting was edited and published by Raven Press. This project has been completed.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: A consensus meeting on the management of children with febrile seizures was held in May, 1980, with the objective of reaching general agreement on the risks of sequelae in children with febrile seizures and the comparison of these risks with the risks and benefits of prophylaxis with anticonvulsants.

Methodology: This conference was part of a consensus development series sponsored by the National Institutes of Health to bring together practicing physicians, research scientists, consumers and others in an effort to assess the available scientific information and to attempt to reach a consensus on a rational approach to management of children with febrile seizures.

Major Findings: The consensus statement concluded that the prognosis for children with febrile seizures was excellent and that there is no evidence that prophylaxis can prevent long-term sequelae.

Significance to NINCDS Program and Biomedical Research: Febrile seizures are common and affect some 3-4% of the population. The findings of the consensus panel essentially have excluded some 60% of all children with febrile seizures from any consideration for treatment. The panel also outlined several areas in need of further research, such as the assessment of the potential cognitive effects of phenobarbital (commonly used in prophylaxis for children with febrile seizures) on young children.

Proposed Course of Contract: With the publication of the monograph "Febrile Seizures", this project has been completed.

Publications:

Febrile Seizures, edited by Karin B. Nelson and Jonas H. Ellenberg, Raven Press, 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02447-02 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

A Prospective Study of Low Birthweight Infants

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. J.M. Dambrosia, Mathematical Statistician, OBFS, NINCDS
P.I. Karin B. Nelson, Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS

COOPERATING UNITS (if any)
Children's Hospital of Washington, D.C.
Section on Cerebral Palsy and Other Motor Disorders, DNB, NDP, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

All low birthweight (1750gm or less) infants referred to Children's Hospital are examined, CAT scanned for hemorrhage, and evaluated by the Hospital staff. Specified information is collected prospectively on each child until the age of three years. The objective of the study is to identify risk factors associated with neurological deficits, in particular CP. This project continues in the planning phase.

Project Description:

Objectives: Collection and analysis of specific data elements from all low birthweight (1750gm or less) children referred to Children's Hospital of Washington, D.C. A major objective of the study is to identify risk factors in these children associated with neurological deficits, in particular the occurrence of cerebral palsy.

Methodology: This project is in the planning phase. Until outcomes and data collection techniques are rigorously established and protocols written for each component of the study, the data analysis method cannot be specified. It has been agreed that all of those children referred to the hospital will be examined by the staff, given a CAT scan for hemorrhage (graded on a scale of 0 to 4), and evaluated for psychological and mental development. A minimum length of follow-up would be three years.

Major Findings: NA

Proposed Course: During FY 1982, study planning will continue, endpoints will be defined, and data collection, examination, and psychological evaluation protocols will be written in order to proceed with the study.

Publications: None.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02409-03 OBFS

PERIOD COVERED
October 1, 1980, through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Image Reconstruction Theory

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Rodney A. Brooks, Physicist, Neuroradiology and Computed Tomography Section, Surgical Neurology Branch, NINCDS
P.I. Alan J. Talbert, Statistician, OBFS, NINCDS

COOPERATING UNITS (if any)

Neuroradiology and Computed Tomography Section,
Surgical Neurology Branch, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Computer simulations of CT scans have been made in the development of an improved method of back projection in computed tomography. This method employs interpolation in both the and coordinates. This project is completed.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: The purpose of this study was to develop and test a new method of back protection for precision and efficiency. A simple geometrical evaluation led us to expect high accuracy from this method.

Methodology: The ϕ interpolation method was examined by using it to do simulated scans on the System 370. The back projection results were written on a tape in a format acceptable to an EMI CT scanner. The tape was then taken to the scanner, and pictures were produced. The picture quality was judged objectively by comparisons of absolute rowsums to absolute rowsums from the simulated phantom. Computation times (in the 370) were measured by means of RHB248, a high precision internal timing subroutine.

Major Findings: The ϕ interpolation method was found to be less precise and considerably slower in computation than the recently discovered phantom views method.

Significance to NINCDS Program and Biomedical Research: This study is a step forward in the understanding and general knowledge of back projection methods. New methods are still appearing frequently. All must be tested objectively before being either adopted or laid to rest.

Proposed Course: This study is now completed.

Publications: None.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02413-03 OBFS

PERIOD COVERED
October 1, 1980, through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Study of Lisuride for the Treatment of Parkinson Patients

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. D. Calne, Chief, Experimental Therapeutics Branch, IRP, NINCDS

Others: R. Gopinathan, Therapeutics Section, Experimental Therapeutics Branch, IRP, NINCDS
James Dambrosia, Mathematical Statistician, Section on Mathematical Statistics, OBFS, NINCDS

COOPERATING UNITS (if any)
Therapeutics Section, Experimental Therapeutics Branch, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.1	.1	0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The study was undertaken to determine the effectiveness of Lisuride for the treatment of Parkinsonism. A reduction of rigidity, tremor, and akinesia was observed. Adverse reactions were also noted. The results of the study appeared in Neurology this year. This project is now completed.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To determine the effectiveness of Lisuride in the treatment of patients with Parkinson's disease in a controlled phase II study.

Methodology: Patients were evaluated weekly by a neurologist for each of three phases of the study: low dose Lisuride, high dose Lisuride, and placebo. A modified Columbia rating scale provided scores for akinesia, rigidity and tremor. Scores for reaction time and gait were obtained by a computer sensor system. Patient responses were compared across phases using analysis of variance and nonparametric methods. All adverse effects were recorded and analyzed.

Major Findings: Lisuride treatment improved most clinical features of Parkinson's disease; the exception was balance. The adverse effects were comparable to those associated with Bromocriptine.

Significance to NINCDS and Biomedical Research: This study provided valuable information on a new drug for the treatment of Parkinson's disease and established a basis for its use in future comparative drug trials. Experience in the use and interpretation of objective computerized evaluation of the clinical features of the disease will enhance future studies.

Proposed Course: Completion of this project established the basis for a randomized controlled clinical trial of Lisuride versus Bromocriptine that trial is now in progress.

Publications:

"Lisuride in Parkinsonism," Neurology, Vol. 31, No. 4, pp. 371-376, April 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02410-03 OBFS

PERIOD COVERED
October 1, 1980, through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Dual Energy Scanning

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Rodney A. Brooks, Physicist, Neuroradiology and Computed Tomography Section, Surgical Neurology Branch, NINCDS
P.I. Alan J. Talbert, Statistician, OBFS, NINCDS
P.I. David G. Morgenthaler, Computer Scientist, Neuroradiology and Computed Tomography Section, Surgical Neurology Branch, NINCDS

COOPERATING UNITS (if any)

Neuroradiology and Computed Tomography Section,
Surgical Neurology Branch, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0	PROFESSIONAL: 0	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Methodology has been implemented for optimizing the use of dual-energy X ray scans to obtain information on chemical constituents of scan subjects. Two papers on this work have been published and a third paper has been submitted. This project is completed.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: The purpose of this study was to compute theoretically optimum energies and doses for application in dual-energy scanning with X ray scanners. The optimization is for minimum noise with maximum differences in absorption at the different energies.

Methodology: At various energy combinations, computations were made to determine noise for both photoelectric and Compton absorption of X rays vs. proportional dose at fixed total dose. The minimum of these values showed the optimum dose proportion between energies. Noise was then measured at various energy combinations at the previously determined optimum dose, in order to find the optimum low energy for minimum noise when using high-energy beams of 80-100 keV. Using equivalent energies and noise factors, the above work was generalized to apply to the polyenergetic spectra obtained from X ray machines.

Major Findings: About half the dose at each energy was found to be optimum. At this dose proportion, for monoenergetic beams, a low-energy value of 40 keV produces minimum noise when using high-energy beams of 80-100 keV. For polyenergetic beams, noise increased about 20% with integral dose equivalence. Noise is minimized by narrow spectra.

Significance to NINCDS Program and Biomedical Research: This work is of interest to researchers and physicians who are using X ray scans to determine chemical constituents of parts of organs. This approach provides valuable physiological details which single-beam absorption scans do not show.

Proposed Course of Work: This study is now completed.

Publications:

Talbert, A., Brooks, R., Morgenthaler, D. "Optimum energies for dual-energy computed tomography," Physics in Medicine and Biology, Vol. 25, No. 2, 1980.

Morgenthaler, D., Brooks, R., Talbert, A. "Noise factor of a polyenergetic X ray beam in computed tomography," Physics in Medicine and Biology, Vol. 25, No. 2, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02312-05 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)
Maternal Infection Study **
(Previously titled "Methodology for Systematic Analysis of Multiple Antibody Readings on Matched Controlled Studies").

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Jonas H. Ellenberg, Chief, Section on Mathematical Statistics, OBFS, NINCDS
John L. Sever, Chief, Infectious Disease Branch, IRP, NINCDS
Other: Alan Talbert, Mathematical Statistician, OBFS, NINCDS
Martha Griswold, Statistician, OBFS, NINCDS

COOPERATING UNITS (if any)

Infectious Disease Branch, IRP, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies, OD

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.3	.3	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Analysis of the Collaborative Perinatal Project (CPP) data continues in the area of maternal infection. [The CPP is a prospective study of approximately 60,000 gravidae and the follow-up of their children through the seventh year of life.] The relationship of maternal infection during pregnancy with the later status of the child is being examined using both clinical and serologically confirmed infections in the mother.

**[This study is the OBFS/NINCDS portion of a larger study entitled: Perinatal Infections Causing Damage to the Child -- Collaborative Perinatal Project. The principal investigator on the overall study is Dr. John L. Sever, Chief, IDB, IRP, NINCDS.]

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To assess the relationship between maternal infection during pregnancy with the outcome of the child, in a large prospective followup study of approximately 60,000 women. The children were followed to seven years of age.

Methodology: Two methodologies have been used, a prospective and a case control approach. A prospective assessment of risk of specified outcome (from birth to seven years of life) was used for all clinically confirmed infections. Since serological confirmation of the common infections occurring during pregnancy on all women in the project would not have been feasible, a case control design has been implemented, assessing the titer of 12 antigens in women with abnormal children, in comparison with matched control women with normal children.

Major Findings: Both the prospective clinical infection study and the case control serological study are in progress. None of the results have been released.

Significance to NINCDS Program and Biomedical Research: The study will provide estimates of risk to the fetus in mothers with infections during pregnancy. This will allow for the comparison of the risk of various forms of intervention as contrasted to these risks.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02480-01 OBFS

PERIOD COVERED
October 1, 1980, through September 30, 1981

TITLE OF PROJECT (80 characters or less)

** A Clinical Study of Bromocriptine and Pergolide for the Treatment of Parkinson's Disease

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. J.M. Dambrosia, Mathematical Statistician, OBFS, NINCDS
P.I. P. Le Witt, Experimental Therapeutics Branch, IRP, NINCDS
P.I. D. Calne, Head, Experimental Therapeutics Branch, IRP, NINCDS

COOPERATING UNITS (if any)
Experimental Therapeutics Branch, IRP, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies, OD

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.20	.15	.05

CHECK APPROPRIATE BOX(ES)
☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project assesses the relative efficacy of Bromocriptine versus Pergolide for the treatment of Parkinson's disease. A randomized, double-blind, two-period crossover trial with washout periods is employed to evaluate treatment of forty outpatients. Patient responses are measured objectively by computer sensing equipment and clinically using a modified Columbia rating scale. Adverse reactions are monitored throughout the trial.

**[This study is the OBFS/NINCDS portion of a larger study entitled: Therapeutic Studies in Parkinsonism and Other Movement Disorders (Z01 NS 02258-05). The principal investigator on the overall study has been Dr. Donald Calne, formerly Chief, Experimental Therapeutics Branch.]

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: Determination of the relative effectiveness of Bromocriptine and Pergolide for the treatment of Parkinson's disease. Adverse effects are monitored, recorded, and compared for the two treatments.

Methodology: A randomized, double-blind, two-period crossover trial with washout between periods is employed to evaluate treatment in forty out-patients with Parkinson's disease. A modified Columbia rating scale and a computerized sensing system are used to provide clinical and objective measurements of patient response to treatment.

Significance to NINCDS and Biomedical Research: The study will provide a valid comparison of effectiveness of the two treatments and information required for future pharmacological and clinical studies of these drugs for the treatment of Parkinson's disease. Differences of adverse effects will be noted and reported at the completion of the study.

Proposed Course: The study is ongoing and is scheduled for completion in January, 1982.

Publications: None.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02481-01 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

The Use of Phantom Views to Diminish an Artifact in CT Scans

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. George H. Weiss, Chief, Laboratory of Physical Sciences, DCRT
P.I. Alan J. Talbert, Statistician, OBFS, NINCDS
P.I. Rodney Brooks, Physicist, Neuroradiology and Computed Tomography Section, Surgical Neurology Branch, NINCDS

COOPERATING UNITS (if any)

Laboratory of Physical Sciences, IRP, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.2	.2	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An artifact in computed tomography scans which occurs with too few views is the appearance of streaks at some distance from the image causing them. The phantom views method consists of inserting phantom data points, obtained by interpolation between real data points. This study shows that the phantom views method does diminish this artifact and finds the optimum number of phantom views. This study has been completed and a paper has been submitted for publication.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: CT scan pictures are subject to some deterioration in quality when when too few views are used. Increasing the number of views increases equipment costs and computing time. For these reasons the number of views used is a compromise, and some of this deterioration is accepted. The objective of this study is to reduce this artifact without increasing the number of real views.

Methodology: By means of simulations done on the System 370, a comprehensive survey was made of all the back projection methods known to us to determine which gave the best pictures for a given number of views, by both subjective and objective standards. Concurrently a mathematical investigation was conducted which described the artifact causing the observed deterioration of picture quality.

Major Findings: The simulated scan study revealed that the phantom views interpolated in ϕ produced the best pictures and that picture quality was improved by the insertion of up to three phantom views between real views, after which computing time requirements began to outweigh picture improvement. The mechanism of the artifact involved was described mathematically and the experimental results were confirmed.

Significance to NINCDS Program and Biomedical Research: The CT industry and other CT research groups pay close attention to such findings. These results have been considered in the design of the PET scanner being built at NIH and will be taken into consideration by scanner research groups everywhere. The results can be applied to existing scanners by updating the software.

Proposed Course of Work: This study is completed.

Publications: None.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02482-01 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

**Optimization of Software for PET Scanner

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Alan J. Talbert, Statistician, OBFS, NINCDS
P.I. Rodney A. Brooks, Physicist, Neuroradiology and Computed Tomography Section, Surgical Neurology Branch, NINCDS

COOPERATING UNITS (if any)

Neuroradiology and Computed Tomography Section
Surgical Neurology Branch, IRP, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies, OD

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.6	.6	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Software is being developed for a PET scanner which is being constructed by the Neuroradiology and Computed Tomography Section. The picture processing program is being optimized for speed and accuracy. This involves the use of low level languages and intimate knowledge of image processing mathematics and the computer architecture. Substantial improvements in execution time have been achieved. A study is under way to determine if the addition of an array processor to the PET computer would improve times by amount sufficient to justify its purchase.

**[This study is the OBFS/NINCDS portion of a larger study entitled: Development of a High Resolution Positron Emission Tomograph." The principal investigator is Dr. Rodney Brooks, Neuroradiology and Computed Tomography Section, Surgical Neurology Branch, IRP, NINCDS.]

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: Image processing in scanners involves a large number of computations and is therefore time-consuming. It is very frustrating to users to wait up to five minutes for a picture after the data has been acquired. The purpose of this work is to reduce by any means the computing time required by the image processing software in the PET scanner being built at NIH. Picture quality must not be sacrificed. In fact, since picture quality is always a compromise in these machines, improvement would be welcome.

Methodology: The reconstruction program is being written first in FORTRAN V. Optimization in speed is being undertaken by several concurrent approaches: a) The FORTRAN is being rewritten for faster time. b) Redundant computations are sought out and eliminated. c) High usage parts of the program are rewritten in assembly language. d) High usage parts are then rewritten in microcode, which is faster than assembly language. e) Fundamentally different and faster methods of computation are sought. f) Precision in calculations is always kept in view and improved when possible. g) The applicability of an array processor to optimization is being investigated. h) The problems involved in microcoding when floating point instructions are involved is being investigated.

Major Findings: The two most time-consuming parts of the reconstruction program (inner loops of back projection and of the convolution filter) have been rewritten in assembly language. It has been discovered that there is a certain complementarity in the index array values for views at complementary angles. It is expected that this will permit combination of these views, affecting a 50% reduction in processing times in preinterpolation and back projection. An integer method of computing indices has been discovered, which has been shown in tests to be more precise than the floating point calculation it may replace. It is expected also to be faster.

Significance to NINCDS Program and Biomedical Research: The integer index calculation method requires microcoding in order to execute efficiently. It will be of great interest to owners of recently manufactured scanners which have computers with the user microcode option. The method of combined complementary views should be of interest to the entire polar view scanner industry.

Proposed Course of Work: This is a long-range project which will continue for many more months.

Publications: None.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02485-01 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Response of cultured postimplantation mouse embryos to potential teratogenic effect of phenytoin and valproic acid

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Albrecht Bruckner, Laboratory of Molecular Biology, NINCDS

Other: Young Jack Lee, Mathematical Statistician, Section on Mathematical Statistics, OBFS, OD, NINCDS
Martha Griswold, Statistician, OBFS, OD, NINCDS

COOPERATING UNITS (if any)

Laboratory of Molecular Biology, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS: .10	PROFESSIONAL: .05	OTHER: .05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Early somite-stage embryos from mice were explanted at the ninth day of gestation and exposed to potential teratogens for 48 hours. The study will measure possible teratogenic effects, if any, that may be manifested in DNA content, protein content, the number of somites, diameter of embryo and crown-to-rump length. This project is completed.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To determine the teratogenicity of phenytoin and valproic acid.

Methodology: Early somite-stage embryos from mice were explanted at the ninth day of gestation and exposed to potential teratogens for 48 hours. Then the following measurements were made: the number of somite, DNA content, protein content, diameter of embryo and crown-to-rump lenpth. The data were analyzed using the analysis of covariance on the rank transformed and original raw data.

Major Findings: Both chemicals showed significant effect on all the outcome variables. The quotient of protein content to DNA content was significantly affected at the highest concentration by phenytoin but not by valproic acid.

Significance to NINCDS Program and Biomedical Research: DPH and VPA are teratogens to mammalian embryos exposed in vitro during organogenesis. At concentrations close to or within therapeutic plasmal levels in man, the degree of the teratogenic response following direct exposure to the drug is dose and stage dependent.

Proposed Course: This project is completed.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02487-01 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Nonparametric confidence limits for survival probabilities and quantiles

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Young Jack Lee, Mathematical Statistician, Section on Mathematical Statistics, OBFS, NINCDS
P.I. Richard Simon, Chief, Biometric Research Branch, National Cancer Institute

COOPERATING UNITS (if any)

Biometric Research Branch, National Cancer Institute

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS: .025	PROFESSIONAL: .025	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Time to occurrence of a defined event (such as death, recurrence of disease, response, etc.) from a reference event is, in clinical studies, characterized by survival probability distributions. Nonparametric confidence limits for survival probabilities and quantiles were studied. The research result will be published in Cancer Treatment Reports and presented as an invited paper at the 1981 Joint American Statistical Association Meetings, in Detroit, Michigan. This project is completed.

Project Description:

Objectives: Development of a simple, easy statistical method for confidence limits of survival probabilities and quantiles.

Methodology: Statistical theory and computer simulation.

Major Findings: Among a number of possible methods, using the Peto estimate of survival probability variance for the confidence limits is simplest, easiest and as effective as other more complicated methods, in particular when the sample size is small.

Significance to NINCDS Program and Biomedical Research: We now have a simple, easy nonparametric method for confidence limits of survival probabilities and quantiles.

Proposed Course of Work: This project is now completed.

Publications: R. Simon and Y.J. Lee, Nonparametric confidence limits for survival probabilities and the median, accepted for publication in Cancer Treatment Reports.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02489-01 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)
** Evaluation of the effectiveness of information services provided to specialists in communicative disorders by MEDLINE

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Christy Ludlow, Communicative Disorders Program, NINCDS
P.I. Barbara Reiner, Communicative Disorders Program, NINCDS
Others: Young Jack Lee, Section on Mathematical Statistics, OBFS, NINCDS
Sylvia Edelstein, Systems Analyst, Section on Computer Applications, OBFS, NINCDS
Karlin Richardson, Programmer, Section on Computer Applications, OBFS, NINCDS

COOPERATING UNITS (if any)
Communicative Disorders Program, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies, OD

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS: .15	PROFESSIONAL: .15	OTHER: 0

CHECK APPROPRIATE BOX(ES)
☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Five study centers are participating in evaluating the effectiveness of MEDLINE in information services provided to specialists in communicative disorders. User profiles and information needs are collected through preuse questionnaires. The data coding form has been developed, and the data management system is being developed using the H-P minicomputer.

**[This study is the OBFS/NINCDS portion of a larger contract study entitled: Evaluation of the Effectiveness of Information Services Provided to Specialists in Communicative Disorders by MEDLINE. The project officer is Dr. Christy Ludlow, CDP, NINCDS. Contract numbers are: N01 NS 0-2342, N01 NS 0-2343, N01 NS 0-2344, N01 NS 0-2345, and N01 NS 0-2346.]

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: The Office of Biometry and Field Studies is collaborating with CDP in the study of MEDLINE service to the communicative disorder specialists. The OBFS is responsible for coding form design, data entry and management system, and statistical analyses.

Methodology: The coding form has been designed so that the data entry can be done directly. The data entry and management will be done using the H-P mini-computer. Once the quality of the data is assured, the data will be transferred to the DCRT, NIH computer. Statistical analyses will be done using the DCRT, NIH computer.

Major Findings: This study is in progress.

Significance to NINCDS Program and Biomedical Research: Better quality control of data, unified treatment of data incoming from five different study centers, and the freeing of CDP scientists from data management are made possible.

Proposed Course of Work: This is a long-term project which will continue into 1983.

Publications: None.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02483-01 OBFS

PERIOD COVERED October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Predictive Value of the EEG in Febrile Seizures

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Jonas H. Ellenberg, Chief, Mathematical Statistics Section, OBFS, OD, NINCDS
Nikola Sofijanov, Pediatric Neurologist, University of Skopje, Yugoslavia
Karin B. Nelson, Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS
Deborah G. Hirtz, Pediatric Neurologist, Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS
Other: Frances Canning, Forms Design, DNB, NDP, NINCDS
Sylvia Edelstein, Senior Programmer, Computer Applications Section, OBFS, NINCDS

COOPERATING UNITS (if any)

Pediatric Clinic, University of Skopje, Yugoslavia

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.10	0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study will evaluate the significance of the EEG as a predictor for recurrence of seizures in those children who have had a simple febrile convulsion. Outcome with respect to febrile seizure recurrence and afebrile seizure occurrence will be reported. The evolution of the EEG pattern will be described, and patterns will be correlated with the clinical outcome. The clinical study is to be carried out in Skopje, Yugoslavia, at the Pediatric Clinic of the University of Skopje.

The study is expected to begin during FY82. Completed during FY'81 were the design of the study and the development of forms and procedures.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To evaluate the significance of the EEG as a predictor for recurrence of seizures in those children who have had a simple febrile convulsion.

Methodology: The health care system in Yugoslavia provides an excellent opportunity for a followup of children with febrile seizures. Given the opportunity for free care and a referral system to a central pediatric clinic in the province province of Macedonia, essentially all children with febrile seizures in the region will be seen at the central clinic. Further, EEG's are routinely given to these children. Approximately 500-700 children with febrile seizures will enter the study over a three-year period and be given EEG's periodically. The evolution of the EEG pattern will be described and patterns will be correlated with the clinical outcome.

Major Findings: This study is in the planning phase. The study has been designed, protocol written and forms developed.

Significance to NINCDS Program and Biomedical Research: An important question arose during the consensus conference on febrile seizures held in May of 1980, as to the usefulness of the EEG in the workup of a child with febrile seizures. This proposal is responsive to this question.

Proposed Course of Contract: The study is expected to begin in FY'82, with patient accrual and followup lasting five years.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02484-01 OBFS

PERIOD COVERED October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

** Statistical Coordinating Center for Communicative Disorders Program projects

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Young Jack Lee, Mathematical Statistician, Section on Mathematical Statistics, OBFS, NINCDS
P.I. Christy Ludlow, Communicative Disorders Program, NINCDS

COOPERATING UNITS (if any)

Communicative Disorders Program, NINCDS

LAB/BRANCH

Office of Biometry and Field Studies, OD

SECTION

Mathematical Statistics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS: .10	PROFESSIONAL: .10	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Statistical designs are being developed and sample sizes determined for three CDP, NINCDS, project plans. They are: a study of the acquisition of communicative skills through speech, sign or total communication in the congenitally deaf; a study to evaluate the outcome of language learning through speech and/or sign in the congenitally deaf; and a population-based cohort study to evaluate the impact and treatment of speech and language disorders in children.

**[This study is the OBFS/NINCDS portion of contract studies in communicative disorders. The project officer of the contracts was to be Dr. Christy Ludlow, CDP, NINCDS. However, these contract studies have not been funded, and therefore, are inactive.]

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To collaborate with CDP in designing projects, developing protocols, data collection and management, and statistical analyses. CDP projects likely to be supported by the Statistical Coordinating Center are: a study of the acquisition of communicative skills through speech, sign or total communication in the congenitally deaf; a study to evaluate the outcome of language learning through speech and/or sign in the congenitally deaf; and a population-based cohort study to evaluate the impact and treatment of speech and language disorders in children.

Methodology: The Statistical Coordinating Center will consist of an operations office, a computer center and a statistics office. The operations office is responsible for direct interactions with the clinical coordinating center, the computer center for system design and data management, and the statistics office for design, analysis and study progress monitoring.

Significance to NINCDS Programs and Biomedical Research: Better quality control of data, constant monitoring of the study progress, and better interactions among project directors, clinical investigators, computer programmers, and statisticians will be possible. It will be also more cost-effective than the statistical coordinating center being a part of individual contracts or grants.

Major Findings: This project is in progress.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02488-01 OBFS

PERIOD COVERED October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Interactive Computer System for Patient Entry and Randomization for Clinical Study

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Young Jack Lee, Mathematical Statistician,
Section on Mathematical Statistics, OBFS, NINCDS

COOPERATING UNITS (if any)

Laurie Burch, Programmer, Personal Service Contract

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	-0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An interactive computer system is under development. The system will utilize the TSO of the DCRT, NIH computer. The clinical trial operations office will register patients entering clinical trials, check the eligibility and perform random allocations of the treatment to eligible patients, all using the interactive system.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: The Office of Biometry and Field Studies is expected to participate in several clinical and field studies including the NDP phenobarbital clinical study. The system will facilitate patient registration (and randomization) and communication with clinical coordinating centers.

Methodology: The TSO function of the DCRT, NIH computer will be used.

Major Findings: The study is in progress.

Significance to NINCDS Program and Biomedical Research: The system will be used for the NDP phenobarbital clinical study, as well as CDP clinical and field studies. The system will also be made available to whoever wants to utilize it inside and outside NINCDS.

Proposed Course of Work: This project will continue through 1981.

Publications: None.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02486-01 OBFS

PERIOD COVERED October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Statistical models of in vitro mutagenicity assays

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Young Jack Lee, Mathematical Statistician, Section on Mathematical Statistics, OBFS, NINCDS

P.I. William J. Caspary, National Toxicology Program, National Cancer Institute

COOPERATING UNITS (if any)

National Toxicology Program, National Cancer Institute

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Chemically-induced genetic damages of cells (mammalian or submammalian) in vitro are observable by allowing the cells to express their DNA damage and the progenies with locus-specific mutation to be selected and form colonies. Statistical models have been studied. The research result has been presented to the Gordon Research Conference on Genetic Toxicology and to other meetings. It will also be presented at the 1981 Joint American Statistical Association Meetings, in Detroit, Michigan.

Project Description:

Objective: Mutation is suspected to be a precursor of genetic disorders and malignancies. Because mutational events are not immediately apparent, short term in vitro assays are utilized to determine potential mutagenicity of a chemical. Chemicals may cause DNA damages which make damaged cells produce progenies with mutational phenotypic expression (i.e. mutants). Because of the cell growth regulation, toxicity and difference in cloning ability, the mutant frequency does not necessarily measure the mutant progenitor frequency without bias or random fluctuations. The project is to relate the mutant progenitor to the mutant progenitor frequency through a mathematical conceptual reconstruction of assays.

Methodology: Mathematical and statistical accounting of experimental steps of assays.

Major Findings: In the mouse lymphoma cell TK locus mutation assays the mutant frequency is shown to be linearly related to the mutant progenitor frequency. For a majority of chemicals tested, the linear coefficient is expected to be one. The inherent variability of the mutant frequency can be estimated, and the statistical classification of mutagenicity of a chemical can be done using the linear relationship.

Siginificance to NINCDS Progams and Biomedical Research: This basic biostatistical research will help understand the relationship among the acute toxicity, DNA damage, phenotypic expression of mutational DNA damage and cloning ability in living cells exposed to chemicals in vitro.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02490-01 OBFS

PERIOD COVERED
October 1, 1980 to September 31, 1981

TITLE OF PROJECT (80 characters or less)

Research in Statistics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Jonas H. Ellenberg, Head, Section on Mathematical Statistics, OBFS, NINCDS
Young Jack Lee, Mathematical Statistician, Section on Mathematical Statistics, OBFS, NINCDS
James M. Dambrosia, Mathematical Statistician, Section on Mathematical Statistics, OBFS, NINCDS
Alan Talbert, Mathematical Statistician, Section on Mathematical Statistics, OBFS, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.65	.65	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project addresses statistical problems generated from collaboration with scientists in other program areas and general statistical problems of current interest. This project is a continuing activity of the Section on Mathematical Statistics.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: There are two objectives assocated with this project. The first objective is the development and improvement of statistical methodology to meet the needs of the Institute for design of experiments and field studies, analysis of data, and statistical modeling of biological processes and phenomena. The second objective is the maintenance of knowledge of new developments in statistics.

Methodology: Current studies for this project are: methods of nonparametric regression, determination of sample size for a clinical trial with multinomial outcome, regression in Poisson data, sequential methods with early stopping, two-period crossover designs for Phase II clinical trials, regression methods for survival data, and Markov modeling of clinical features of Parkinson's Disease.

Major Findings: A statistical model relating mutational events to phenotypic expression was developed for in vitro mutation assays. These results were presented at the 1981 Gordon Research Conference.

Significiance to NINCDS and Biomedical Research: This project will improve and develop statistical methods applicable to Institute research.

Proposed Course: Continuing

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02491-01 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Activities of Daily Living Following Stroke

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I: P. Wolf, Department of Neurology, Boston University
J. Dambrosia, Mathematical Statistician, Section on Mathematical Statistics, OBFS, NINCDS
Others: I. Fishman, Statistician, Computer Applications Section, OBFS, NINCDS
S. Kunitz, Head, Computer Applications Section, OBFS, NINCDS

COOPERATING UNITS (if any)
Dept. of Neurology, Boston Univ.; Dept. of Neurology and Neurosurgery, Univ. of Maryland; Dept. of Neurology, Univ. of South Alabama; Dept. of Neurology, Duke Univ.; Medical Center, Stanford Univ.

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.15	.10	.05

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study attempts to establish the scores associated with activities of daily living as a measure of stroke outcome. This study is a component of the Pilot Stroke Data Bank Project. The influence of factors such as medical complications, age, site and type of lesion, on the stroke course and subsequent level of activities of daily living and performance and placement class of the patients will be examined at specific points in time. Each patient is expected to have a minimum of two years of follow-up.

Project Description:

Objectives: The study objectives include the following: Determination of the effects of site and type of lesion on the patient's course and the final level of the patient's functional ability, determination of the effects of medical complications on the progression of a patient's activities of daily living (ADL), and determination of the relationship of ADL to the patient's placement and performance disposition.

Methodology: This study is one of many projects from the Pilot Stroke Data Bank Project. Patients are classified by stroke type, lesion location, age, sex, performance class, and placement class. ADL scores at specified points in time relative to the patient's entry into the study are analyzed relative to various classification categories. Descriptive and graphic statistical methods are applied to the data to provide information regarding stroke course conditional on factors that may influence outcome.

Major Findings: This study is in progress.

Significance to NINCDS and Biomedical Research: The progression of stroke from onset to post discharge patient disposition provides valuable information, not only as an end in itself, but for planning and designing future studies concerning intervention into the stroke course, as well as, identification of both patient type and factors to be taken into account as indicators for prognosis.

Proposed Course: Exploratory data analysis and data verification will continue through August 1981. The Pilot Stroke Data Bank, at that point in time, will have data on approximately 900 (non-TIA) stroke patients. Work will continue on this project through FY'82, with expected completion in FY'82.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02492-01 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Data Support for Diagnostic Algorithms of Stroke

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J.P. Mohr, Head, Department of Neurology, University of South Alabama
C. Kase, Department of Neurology, University of South Alabama
J. M. Dambrosia, Mathematical Statistician, Section on Mathematical Statistics, OBFS, OD, NINCDS
Others: I. Fishman, Statistician, Computer Applications Section, OBFS, NINCDS
S. Kunitz, Head, Computer Applications Section, OBFS, NINCDS

COOPERATING UNITS (if any) Dept. of Neurology, Boston Univ., Dept. of Neurology and Neurosurgery, Univ. of Maryland; Dept. of Neurology, Duke Univ.; Dept. of Neurology, Univ. of South Alabama; Medical Center Stanford Univ.

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.20	.15	.05

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Pilot Stroke Data Bank project has developed operational diagnostic algorithms for the classification of stroke type. This study utilizes data from the Stroke Data Bank to measure the operational uniformity and consistency of the application of the diagnostic algorithms to patients entered at the four participating stroke centers. Identification of factors common within a stroke type as well as factors that differ between stroke types provides a means for enhancement and verification of the algorithms.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: This study compares the patients with the same stroke type diagnosis with respect to stroke onset, stroke course, neurological examinations, source of diagnosis (CT, angiography, etc.), and outcome. Similar comparisons are made on patients with different stroke type diagnoses. The results will provide information that supports and can be used to enhance the diagnostic algorithms of the Stroke Data Bank project. The main objective of the study is to provide information for the development of an operationally consistent method of stroke diagnosis for use in each Stroke Data Bank Center.

Methodology: Data from the Pilot Stroke Data Bank project are utilized to determine the extent of similarity of patient profiles within each stroke type classification. Patient profiles are also compared between stroke type classifications. Descriptive and graphic statistical methods are applied to the data to provide information either supporting the algorithms or indicating the need for refinement of the algorithms.

Major Findings: This study is in progress.

Significance to NINCDS and Biomedical Research: The development of algorithms for the diagnosis of stroke type that can be operationally and consistently applied at different stroke centers is a basic requirement for any multiple center study of stroke. These diagnostic algorithms provide a measure of intercenter comparability that is necessary for the planning and design of focused clinical studies.

Proposed Course: Exploratory data analysis and data verification will continue through August 1981. The Pilot Stroke Data Bank, at that point in time, will have data on approximately 900 (non-TIA) stroke patients. Work will continue on this project through FY'82 with expected completion in FY'82.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02114-08 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Etiology and Natural History of Convulsive Disorders and Cerebral Palsy

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Jonas H. Ellenberg, Chief, Section on Mathematical Statistics, OBFS, OD, NINCDS

P.I.: Karin B. Nelson, Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS

COOPERATING UNITS (if any)

Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.2	.9	.3

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study examines the relationship between perinatal and early postnatal factors and the occurrence of seizure disorders and cerebral palsy in childhood. The project derives from the data of the Collaborative Perinatal Project, a large prospectively followed population (approximately 60,000 mothers, with their children followed to seven years of age). The univariate screen of maternal, obstetric and pediatric risk factors, and demographic analysis have been completed. Multivariate assessment of the data bank is in progress including correlation and regression analysis. Selected topics of particular clinical relevance are under examination.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To study the relationship between perinatal and early postnatal factors and occurrence of seizures disorders and cerebral palsy in childhood. The project derives from the data of the Collaborative Perinatal Project, a large prospectively followed population (approximately 60,000 mothers, with their children followed to seven years of age).

Methodology: The data bank for this project, involving some 75 million pieces of information has extensive data from structured examinations given during pregnancy and during the first seven years of life of the children. In order to deal with the massive nature of the data base a phased statistical approach to analysis was used. An initial univariate screen delineated those variables with little apparent relevance to the outcome from those with potential for further examination. This was followed with a multivariate assessment of the remaining variables.

Major Findings: Several results relating to the natural history of these disorders as well as predictors of these outcomes have been found. For example, low Apgar scores, especially those at ten minutes and therafter, are powerful predictors of cerebral palsy. The identification of high risk infants in the first minutes of life makes it possible to consider therapeutic intervention.

Significance to NINCDS Program and Biomedical Research: The results of this study have and will continue to be useful in the design of future research studies which rely heavily on assumptions concerning natural history of cerebral palsy and seizures disorders. For example, the use of apgar score in the prediction of outcome in term weight children is being used in the design of a study for prophylaxis against hypoxic ischemic encephalopathy.

Proposed Course of Contract: The major analysis are expected to be completed in Fy'82. The monograph based on these analysis are expected to be completed in FY'83.

Publications:

Nelson, K.B. and Ellenberg, J.H. Apgar Scores as Predictors of Chronic Neurologic Disability. Pediatrics, July 1981.

Ellenberg, J.H. and Nelson, K.B. Predictions of Cerebral Palsy at Four Months of Age. Developmental Medicine and Child Neurology, 1981 (with Editorial Comment).

Nelson, K.B. and Ellenberg, J.H. Febrile Seizures, in Childhood Epilepsy, PSC Publishers, Littleton, Massachusetts, 1981.

Ellenberg, J.H. and Nelson, K.B. Published Recommendations for the Treatment of Febrile Seizures: Their Efficiency vs. Epilepsy. Presented at the Consensus Meeting on the Long-term Management of Children with Febrile Seizures, National Institutes of Health, May 1980. To be published in Febrile Seizures, Raven Press, 1981.

Nelson, K.B. and Ellenberg, J.H. The Role of Recurrences in Determining the Outcome in Children with Febrile Seizures. Presented at the Consensus Meeting on the Long-term Management of Children with Febrile Seizures, National Institutes of Health, May 1980. To be published in Febrile Seizures, Raven Press, 1981.

Nelson, K.B. and Ellenberg, J.H. editors, Febrile Seizures, Raven Press, 1981

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02354-04 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Clinical Trial of Efficacy of Phenobarbital as Prophylaxis for Children with Febrile Seizures

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Karin B. Nelson, Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NINCDS
P.I. Roger J. Porter, Chief, Epilepsy Branch, NINCDS
P.I. Jonas H. Ellenberg, Head, Section on Mathematical Statistics, OBFS, NINCDS

COOPERATING UNITS (if any)
Cerebral Palsy and Other Motor Disorders Section, Developmental Neurology Branch, NINCDS
Epilepsy Branch, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.0	.0	.0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Six percent of all children with febrile seizures are at relatively high risk for later nonfebrile activity. A proposal was considered for a clinical trial which would examine the efficacy and toxicity of chronic and short-term prophylaxis for this group of children. At present chronic prophylactic medication is recommended by several authors without available information as to the potential success or side effects of such medication. At a recent consensus conference on febrile seizures, the panel concluded that there is no evidence to support the concept that prolonged therapy with anticonvulsants prevents the development of epilepsy or significant neurological deficits. The Developmental Neurology Branch, the Epilepsy Branch, and the Office of Biometry and Field Studies have collaborated on this project.

Consideration of this trial has been suspended and no new initiative is expected in the next fiscal year.

PHS-6040
(Rev. 2-81)

Project Description:

Six percent of all children with febrile seizures are at relative high risk for later nonfebrile seizures. A proposal was considered for a clinical trial which would examine the efficacy and toxicity of chronic and short-term prophylaxis for this group of children.

Methodology: A controlled randomized clinical trial was selected as the mechanism for testing the efficacy of phenobarbital.

Major Findings: This project has not been implemented and the planning has been suspended.

Significance to NINCDS Program and Biomedical Research: At a recent consensus conference on febrile seizures, the consensus panel concluded that there is no evidence to support the concept that prolonged therapy with anticonvulsants prevents the development of epilepsy or significant neurological deficits. They recommended continued efforts to clarify the role of anticonvulsant treatment in febrile convulsions.

Proposed Course of Work: No further work is expected in the next fiscal year.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02449-02 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Epidemiology of Disabling Headache

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Murray Goldstein, D.O., M.P.H., Deputy Director, NINCDS, NIH
P.I. Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBFS, NINCDS

COOPERATING UNITS (if any)
None

LAB/BRANCH
Office of the Director and Office of Biometry and Field Studies

SECTION
Office of the Deputy Director and Office of the Chief (OBFS)

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0	0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An extensive collection and review of the published literature and reports on various aspects of epidemiology of Headache has been carried out in FY 1980. Strengths and inadequacies of the published information about prevalence, the characteristics of the afflicted population and the identification of risk factors that may be associated with both the occurrence of the headache syndrome or with its acute exacerbations were summarized and evaluated. Research approaches which can provide improved data for approaching the clinical issues of etiology, prevention and therapy were suggested. An invited paper of the review work was presented at the International Headache symposium 1980 in Florence, Italy, in March, 1980. This study has been completed.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To provide an updated report of the current epidemiological knowledge on disabling headache.

Methodology: The medical and epidemiological literature of headache disorders was extensively reviewed and summarized in the report. Recommendations for future investigations in this area was given.

Major Findings: Emphasis in this review was indicated on the need of an international effort to develop an uniform classification of headache, and prospective studies to investigate various etiological and precipitating factors.

Significance to NINCDS Program and Biomedical Research: Headache research is an area of interest in the NINCDS program.

Proposed Course: This work has been completed.

Publications: Goldstein, M. and Chen, T.C., Epidemiology of Disabling Headache. Proceedings of the First International Headache Conference, Raven Press, N.Y., 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02448-02 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Supraorbital Opacity Pulses During Carotid Artery Compression:
A Method for the Detection of Carotid Obstruction

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. William L. Howell, M.D., Chief Cardiologist, Washington Clinic
P.I. Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBFS, NINCDS

COOPERATING UNITS (if any)
Department of Neurology, Methodist Hospital, Houston, Texas
Department of Vascular Surgery, Walter Reed General Hospital, Wash., D.C.

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0	PROFESSIONAL: 0	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Photoelectric plethysmography was employed to record amplitude changes in pulsatile blood flow from each of the supraorbital fields during carotid compression in 75 patients scheduled for carotid angiograph. A testing method was developed on the basis of these data to detect carotid obstructive patients. The study result showed that with the developed method, 67 percent of the patients with radiologically significant carotid obstruction and 91 percent without it were correctly identified. It suggests that the developed method provides a rapid non-invasive test for unilateral carotid stenosis or occlusion. A report of this study was published in the March issue of the IEEE Transactions on Biomedical Engineering, 1980. This study has been completed.

Project Description:

Objectives: To develop a simple, and non-invasive method of detection of internal carotid occlusive disorders.

Methodology: Patients from two clinics scheduled for angiograms were the subjects of this study. Blood flow at the supraorbital areas was monitored by the photoplethsymography prior to and during carotid artery compression.

Major Findings: The data were quantified and analyzed statistically to derive a test criterion for the detection of internal carotid occlusion. The results showed that the developed method is an efficient one feasible to clinical examination.

Significance to NINCDS Program and Biomedical Research: This study is significant to cerebral vascular disease research.

Proposed Course: This work has been completed.

Publications: Howell, W.L. and Chen, T.C., Supraorbital Opacity Pulses During Carotid Artery Compression - A Method for the Detection of Carotid Obstruction. IEEE Transaction on Biomedical Engineering, Vol. BME-27, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02415-03 OBFS

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Cage Standards for Primates

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Dr. William T. London, Chief, Experimental Pathology Section,
IDB, IRP, NINCDS

Other: Dr. James Dambrosia, Mathematical Statistician, Section on
Mathematical Statistics, OBFS, OD, NINCDS

COOPERATING UNITS (if any)

Infectious Diseases Branch, IRP, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies, OD

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0	0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Present cage assignments for primates are based solely on the animals' weight. Variation in shape between species of primates of the same weight indicate that the current weight-based standard may be inappropriate. A large number (410) of primates of four different species have been measured (arms, legs, chest, tail, crown to rump, crown to heel) in order to determine association of and variations in weight as functions of shape measurements. This study has been temporarily suspended.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: Determinations of allometric equations for four species of nonhuman primates.

Methodology: Four species of primates (chimpanzee, rhesus, patas, and cebus appella) were used to obtain six physical linear measurements for comparison with the animal's weight. The allometric equations for each specie was determined from data collected on 347 animals by methods of least squares.

Major Findings: Data analysis has not been completed at this time.

Significance to NINCDS Program and Biomedical Research: Development of confidence bands on the allometric equations would enable one to accurately estimate intra and interspecies differences and similarities when only the total body weights are known.

Proposed Course: The course of this project is unknown at this time due to changes in personnel.

Publications: None

TAB 2 -- EXTRAMURAL ACTIVITIES PROGRAM -- EAP

ANNUAL REPORT

October 1, 1980 through September 30, 1981

Extramural Activities Program

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ADMINISTRATIVE SUMMARY 1

RESEARCH GRANTS PROGRAM 2

MANPOWER PROGRAMS' REPORT 5

GRANTS MANAGEMENT SUMMARY 7

CONTRACTS MANAGEMENT SUMMARY 8

OFFICE OF DATA ANALYSIS AND REPORTS 9

SCIENTIFIC EVALUATION SUMMARY 10

ANNUAL REPORT
October 1, 1980, through September 30, 1981
Director's Report
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Extramural Activities Program (EAP), NINCDS, was organized in July, 1975, to serve as the Institute center for science administration and fiscal management of the grant, fellowship, and research contract programs. The structure of EAP includes components responsible for manpower, scientific merit review, contract management, grants management, committee management, data reporting and analysis, and program support services including processing.

The senior staff of EAP consists of:

Director
Deputy Director
Chief, Scientific Evaluation Branch
Chief, Contracts Management Branch
Chief, Grants Management Branch
Chief, Office of Data Analysis and Reports

Staff carries out an overall coordinating and supervisory function in regard to the implementation of recommendations of the NANCDS Council and Contract Advisory Committees, and the processing and issuance of proposals and awards in the respective program areas. The Director, EAP, in consultatation with the Director of NINCDS, works closely with the other Program Directors on questions of policy relating to the NINCDS extramural programs.

More specifically, the Extramural Activities Program coordinates grant and contract programs for the NANCDS Council, the Program Directors, the Contract Review Board, the Training Board, the Program Staff, and the Extramural Staff. The EAP studies and supervises certain program processes, e.g., distribution of awards during the four quarters of the fiscal year; prepares summary data, e.g., the Research Grant and Fellowship Data Books; and provides fiscal information, e.g., Fiscal Status Reports, Percentage Funding Rates, and develops alternate strategies for various budget levels.

One major personnel change is as follows: Mr. Lee Vickers, formerly Computer Systems Analyst, Health Resources Administration, has been named Chief, Office of Data Analysis and Reports. Mr. Vickers replaces Mrs. Charlotte Karel, who retired earlier in the year.

In summary, the Extramural Activities Program provides for the Director of the Institute and the Directors of the Program Areas scientific, fiscal, and administrative management support services.

ANNUAL REPORT
October 1, 1980, through September 30, 1981
Research Grants Program
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Research Grants portion of the NINCDS Annual Report provides an overall summary of administrative developments as they pertain to research grants. Other activities such as training awards, contracts, etc., are mentioned here merely to provide an overview, and are discussed in more detail elsewhere.

The research grant, contract, and training programs of the NINCDS are focused on the identification, stimulation, and support of essential research problems aimed at the improved diagnosis, treatment, and prevention of disorders of the nervous system, the neuromuscular apparatus, the ear, and human communication. They include disorders affecting the development and maturation of the nervous system (developmental disorders, motor and convulsive disorders, and demyelinating and degenerative disorders); disorders caused by extrinsic insults (central nervous system infections, stroke, trauma, neoplasms); and disorders in human communication (hearing, speech, language, the vestibular system, other senses, and behavior). Research support is also provided in the area of fundamental neuroscience which is appropriate to the Institute's mission, but not related to any specific disorder. Included are nerve structure and function studies and investigations of the development of various types of prostheses. The administrative instruments used to accomplish these purposes include research projects, research program projects, clinical research centers, research career awards, research career development awards, teacher-investigator awards, institutional research fellowship awards, individual research fellowship awards, and contracts.

The following Table shows the number of research grant applications considered by the Council at its spring meetings over the past five years.

MAY '77	MAY '78	MAY '79	MAY '80	MAY '81
574	600	645	618	685

Over the past five years, there has been a significant increase in the number of applications reviewed. This may be attributed partially to the effectiveness of the research training programs of the Institute from which the output of fully trained investigators has reached its full potential only in recent years.

The following Table shows the number of research grants awarded and the total amounts of funds expended (in millions) each year for the past five years.

	FY '77	FY '78	FY '79	FY '80	FY '81
NUMBER	1,154	1,284	1,554	1,697	1,683
DOLLARS	$99.0	$110.9	$138.4	$160.5	$178.3

During the current fiscal year there was an eleven percent increase in funds available for the support of research grants. However, there was a slight decrease in the number of grants awarded during the same period. This can be attributed to the continuing high rate of inflation, increases in indirect costs, and other increases in the cost of conducting biomedical research.

Table I (on the following page) shows the number of awards and the amounts of funds expended for each type of award within each Program Area.

TABLE I

Number of Awards and Dollars* Expended by Program Area and Type of Award

	PROGRAM AREAS									
	CD		FN		ND		ST		TOTAL	
TYPE OF AWARD	No.	Dollars	No.	Dollars	No.	Dollars	No.	Dollars	No.	Dollars
Research Grants	256	$ 21.422	385	$ 28,885	598	$ 49.970	170	$ 15.519	1409	$ 115.796
Program Projects and Clinical Centers	20	12.425	10	3.096	29	17.786	36	22.012	95	55.319
Contracts	12	1.670	20	2.630	16	3.730	12	1.500	60	9.530
Training Grants	14	.827	24	2.007	19	1.589	5	.408	62	4.831
Fellowships	46	.953	91	1.778	63	1.322	24	.347	224	4.400
Teacher Investigator Awards	21	.823	0	0	53	2.245	21	.889	95	3.957
Research Career Development Awards	20	.763	22	.840	30	1.128	12	.452	84	3.183
Research Career Awards	1	.033	0	0	3	.096	1	.032	5	.161
GRAND TOTAL	390	38.916	552	39.236	811	77.866	281	41.159	2034	197.177

*Dollars in millions

October 1, 1980 - September 30, 1981

ANNUAL REPORT
October 1, 1980 through September 30, 1981
Manpower Programs' Report
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Institute has four training programs. Two programs, the Individual National Research Service Award Program and the Institutional National Research Service Award Program, are funded from the $9,212 million available in the FY '81 budget for training. The other two programs, the Research Career Development Award Program and the Teacher Investigator Development Award Program, are funded from FY '81 funds available for research grants in the "other" category.

The National Research Service Award Program for Senior Fellows is now in its second year of operation. The Institute has made four awards totalling $101,280 during this period. It is expected that a larger number of awards will be made in future years as this program becomes more visible.

The remainder of this report concerns the specifics of the four program areas:

National Research Service Awards for Institutional Grants (Training Grants)

From FY '81 funds, the Institute provided continuation support for 58 NRSA programs and made 8 new and renewal awards to support the following number of programs, according to NINCDS Program Area:

Program Area	New, Renewal & Supplemental Awards		Continuation Awards		Total	
	Number	Amount*	Number	Amount*	Number	Amount*
Communicative Disorders	2	$ 85	13	$ 742	15	$ 827
Fundamental Neurosciences	1	101	23	1,906	24	2,007
Neurological Disorders	3	93	18	1,496	21	1,589
Stroke and Trauma	2	91	4	317	6	408
Total	8	370	58	4,461	66	4,831

*Amounts in thousands

In the training grant program, funds are being provided for 47 predoctoral trainees and 174 postdoctoral trainees. In addition, about 76 short-term trainees were supported in summer programs.

National Research Service Awards for Individual Postdoctoral Fellows (Fellowships)

From FY '81 funds, the Institute provided continuation support for 130 fellows and made 123 new and renewal awards. A number of supplemental awards were also made but this did not increase the number of individuals being trained. NINCDS made awards to support the following number of fellows, according to NINCDS Program Area:

Program Area	New, Renewal & Supplemental Awards		Continuation Awards		Total	
	Number	Amount*	Number	Amount*	Number	Amount*
Communicative Disorders	20	$ 392	29	$ 561	49	$ 953
Fundamental Neurosciences	50	834	52	944	102	1,778
Neurological Disorders	38	614	38	708	76	1,322
Stroke and Trauma	15	132	11	215	26	347
Total	123	$1,972	130	$ 2,428	253	$ 4,400

*Amounts in thousands

Research Career Development Award Program

During the period covered by this report, NINCDS made the following number of new and continuation RCDAs, according to the NINCDS Program area:

Program Area	New Awards		Continuation Awards		Total	
	Number	Amount*	Number	Amount*	Number	Amount*
Communicative Disorders	2	$ 73	18	$ 690	20	$ 763
Fundamental Neurosciences	6	233	16	607	22	840
Neurological Disorders	1	31	29	1,097	30	1,128
Stroke and Trauma	0	0	12	452	12	452
Total	9	$ 337	75	$2,846	84	$3,183

*Amounts in thousands

Teacher Investigator Development Award Program

During the period covered by this report, NINCDS made the following number of new and continuation TIDAs, according to NINCDS Program Area:

Program Area	New Awards		Continuation Awards		Total	
	Number	Amount*	Number	Amount*	Number	Amount*
Communicative Disorders	4	$ 165	17	$ 658	21	$ 823
Fundamental Neurosciences	0	0	0	0	0	0
Neurological Disorders	49	2,079	4	166	53	2,245
Stroke and Trauma	6	250	15	639	21	889
Total	59	$2,494	36	$1,463	95	$3,957

*Amounts in thousands

ANNUAL REPORT
October 1, 1980 through September 30, 1981
Grants Management Branch
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Grants Management Branch (GMB) consists of two sections, the Grants Administration Section and the Grants Processing Section. There are 22 people in the Branch, with eleven in each section.

During Fiscal Year 1981, the GMB was responsible for a total grant budget in excess of $189 million, of which approximately $180 million was for research and $9 million was for training, or a 7.5% increase from Fiscal Year 1980 in the total grant budget. During Fiscal Year 1981, it is anticipated that approximately 2,250 awards will be issued.

During Fiscal Year 1981, the GMB was responsible for processing a total of approximately 2,006 applications for review at the three annual NANCDS council meetings. Since 1977 the number of applications that the GMB has processed annually for the NANCDS Councils has increased by 33% (from 1,509 to 2,006 applications). During this same period, the number of awards issued by the Branch has increased by 51% (from 1,490 to 2,250). Although the workload for the GMB has substantially increased since Fiscal Year 1977 as demonstrated by these figures, the number of employees in the Branch has decreased during the same period.

In order to continue to absorb the significant increases in workload, two significant changes were initiated during Fiscal Year 1981. One change was to reduce the number of council books being prepared from approximately 600 books per council meeting to 446 books per council meeting or approximately 462 fewer council books per fiscal year. This results in a savings of time and reproduction costs plus allows council members and NINCDS staff to receive the council books earlier. The second change was the reorganization of the Grants Processing Section. This section is now divided into two teams on a program basis similar to that of the Grants Administration Section. This similarity in organizational structure is designed to foster increased efficiency within the GMB plus allow dramatic temporary increases in workload to be handled more effectively.

ANNUAL REPORT
October 1, 1980, through September 30, 1981
Contracts Management Branch
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Contracts Management Branch (CMB) consists of the Chief of the Branch, four contract specialists, and three supporting staff.

During fiscal year 1981, the CMB was responsible for some 85 contracts and interagency agreements, totaling $14 million in awards. The total value of these contracts, including amounts obligated to-date, is nearly $60 million. There are 22 ongoing intra- and interagency agreements, some of which are funded from other sources not included in the dollar amount above. In addition, there are some 86 research contracts that have expired and are in the process of being administratively closed out.

During fiscal year 1981, the CMB issued 18 Request for Proposals (RFPs) for the purpose of soliciting new contract projects and for recompeting several ongoing projects. It is expected that approximately 21 new contract awards will be made during the year due to anticipated multiawards as a result of more than one of these solicitations. Added to this workload are 60 renewals of existing contracts with additional funding and over 100 other actions modifying contracts in some manner but not requiring additional funding.

This year saw the introduction to NINCDS of a new contract mechanism, the Master Agreement. Under this mechanism, a group of organizations deemed qualified to perform one or more of a series of clinical trials will sign agreements--with no funds provided at the time--in order to be eligible to compete for future Task Orders to accomplish the requirements of each category. When a task, or clinical trial, is ready for solicitation, only those organizations with master agreements will be asked to submit competitive proposals for the conduct of each task. Proposals for each task will receive technical merit review and NINCDS Contract Review Board consideration in accordance with usual R&D procurement procedures. The Master Agreement mechanism is being implemented to add flexibility to the Program areas and to speed the procurement process. By the end of FY 1981, it is anticipated that 24 Master Agreements and at least two Task Orders will have been awarded.

FY 1981 ANNUAL REPORT
October 1, 1980 through September 30, 1981
Office of Data Analysis and Reports
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

In the past year the Office of Data Analysis and Reports was affected by several major personnel changes. The Chief of the Office retired and a computer programmer and budget assistant left. All were replaced during this period. The staff now consists of 4 program analysts, a budget assistant, 2 computer programmers, 2 grants clerks and a clerk-typist.

The Office continues to publish a complete series of fiscal and currently active data books. These include on an annual basis the Training Data Book, the Fiscal Year Summary Book Series (4 volumes) and the NINCDS Index to Research Grants and Contracts and on a semi-annual basis the Research Grants Data Book. This year a fourth volume was added to the Fiscal Year Summary Book series. It contains all of the tables previously found in the three volumes and in addition, several new tables --one by program and type and one overall by state and country. The Office conducted a survey of recurring report needs for each of the program areas. Following meetings with each group a schedule for these reports was sent to all program area staff members. This list included types of reports, e.g. currently active, monthly, fiscal, Council etc., with data layout and frequency of distribution .

Several employees have received training in various job-related areas: IRS (Inquiry and Reporting System), Managing and Processing Data Sets at NIH, Principles and Use of CRISP System, Extramural Training Design Team Workshop, Introduction to Supervision and Introduction to the Extramural Programs at NIH.

Two employees received awards this year-- one cash award and one QSI award.

During FY 1981 this office responded to more than 300 requests for information not only from our Institute but from other NIH Institutes and Federal and non-Federal agencies.

ANNUAL REPORT
October 1, 1980 through September 30, 1981
Scientific Evaluation Branch
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Scientific Evaluation Branch (SEB) is responsible for the technical merit review of applications for Research Program Projects, Specialized Centers, Conferences, Teacher-Investigator Development Awards, and Institutional National Research Service Awards. The Branch has three standing Committees -- Communicative Disorders Review Committee (CDRC), Neurological Disorders Program Project Review A Committee (NSP-A), and Neurological Disorders Program Project Review B Committee (NSP-B). Although these three committees are responsible for the technical merit review of the majority of grant applications, it is necessary to convene a number of ad hoc committees to evaluate applications not assigned to a standing committee and to evaluate all contract proposals submitted in response to a "Request for Proposal."

On September 30, 1981 the staff of the Scientific Evaluation Branch included the following individuals:

Ellen G. Archer, Executive Secretary, NSP-B
Alfred Bruner, Executive Secretary
Diane Casillas, Grants Assistant
Margaret Caudle, Grants Technical Assistant
Leon J. Greenbaum, Jr., Executive Secretary, NSP-A
Frances Hisaoka, Grants Assistant
Joyce Lamb, Grants Technical Assistant
Katherine Phillips, Grants Technical Assistant
Meigs L. Ranney, Lead Contracts/Grants Technical Assistant
Raymond Summers, Chief
Howard Weinstein, Executive Secretary
Arthur B. White, Executive Secretary
Olga Williams, Grants Clerk

(Vacant) Executive Secretary, CDRC

During the summer we had one summer employee, Mr. Janson Kelly, Jr.

The following table summarizes the number and type of grant applications that were reviewed, according to the type of review committee, and it indicates the number of site visits that were made.

NUMBER OF APPLICATIONS REVIEWED AND SITE VISITS MADE BY SCIENTIFIC EVALUATION BRANCH ACCORDING TO TYPE OF APPLICATION

Type of Grant Application	Review by Standing NINCDS Committees (CDRC, NSPA and NSPB)	
	Number of Applications	Number of Site Visits
Program Project (P01)	49	39
Specialized Center (P50)	18	10
Cooperative Clinical Research Grant (R10/R01)	2	2
Conference Grant (R13)	12	0
Teacher-Investigator Development Award (K07)	50	0
Institutional National Research Service Award (T32 & T35)	32	0
TOTAL	163	51

The table shows that 163 grant applications were reviewed and that 51 site visits were made.

Concerning the technical merit review of contract proposals that were submitted in response to RFP's, 99 were received in response to 16 RFP's and the evaluation of these proposals involved one site visit. Responses are due for one additional RFP (81-15) before the end of the fiscal year.

Personnel in the Scientific Evaluation Branch work closely with all components of the Extramural Activities Program and with personnel in the four NINCDS programs. It is imperative that we maintain liaison with leaders of the scientific community for the purpose of identifying the most qualified individuals to serve on our technical merit review committees and panels.

ANNUAL REPORT
October 1, 1980 through September 30, 1981
Communicative Disorders Program
National Institute of Neurological and
Communicative Disorders and Stroke

TABLE OF CONTENTS

PROGRAM SUMMARY 1-9

GRANTS ACTIVITY SUMMARY

Taste and Smell

- Introduction 10
- Normal Structure and Function 10
- Abnormal Structure and Function 12

Touch

- Introduction 13
- Normal Structure and Function 13
- Abnormal Structure and Function 14

Hearing

- Structure and Function 15
- Psychoacoustics 15
- Treatment and Management of Hearing Impairment 19
- Vestibular 20

Speech and Language

- Speech Articulation 23
- Speech Motor Control 23
- Speech Disorders 24
- Speech Perception 24
- Laryngeal Pathology 25
- Neurobiology of Language 25
- Adult Aphasia 25
- Dyslexia 26
- Developmental Language Disorders 26
- Sign Language Studies 27

CONTRACT NARRATIVES

Study of Auditory Sensitivity in Young Children (NO1-NS-5-2313) 28

A Comprehensive Study of the Language Recovery Process in Adults with Aphasia Following a Cerebrovascular Accident (NO1-NS-7-2378) 29

Evaluation of a Test of Speech Perception in Noise (NO1-NS-7-2380) 31

Decongestant/Antihistamine Therapy for Otitis Media with Effusion (OME) (NO1-NS-8-2384) 32

Laryngeal Carcinoma: Identification of High Risk Factors (NO1-NS-8-2399) 33

The Acquisition of Language and Communicative Skills by Speech and Sign in Infantile Autism (NO1-NS-9-2305) 35

Evaluation of the Outcome of Preschool Impairment in Language Development (NO1-NS-9-2322) 37

Efficacy of Adenoidectomy/Tympanostomy Tubes for Persistent Otitis Media with Effusion (NO1-NS-0-2328) 38

Determination of Effects of Hearing Aid Amplification on Children (NO1-NS-0-2329) 40

Methods for Studying Phonatory and Articulatory Control in Young Children Who Stutter (NO1-NS-0-2331) 41

Evaluation of the Effectiveness of Information Services Provided to Specialists in Communicative Disorders by MEDLINE (NO1-NS-0-2342) 43

Evaluation of the Effectiveness of Information Services Provided to Specialists in Communicative Disorders by MEDLINE (NO1-NS-0-2343) 45

Evaluation of the Effectiveness of Information Services Provided to Specialists in Communicative Disorders by MEDLINE (NO1-NS-0-2344) 47

Evaluation of the Effectiveness of Information Services Provided to Specialists in Communicative Disorders by MEDLINE (NO1-NS-0-2345) 49

TAB 3 -- COMMUNICATIVE DISORDERS PROGRAM -- CDP

Evaluation of the Effectiveness of Information Services Provided to Specialists in Communicative Disorders by MEDLINE (N01-NS-0-2346) 51

An Analytical Study of the Auditory Effects of Noise (N01-NS-1-2381) 53

High Frequency Hearing Assessment (RFP-NIH-NINCDS-81-05) To Be Awarded in FY 1981 54

PROJECT REPORTS

Characteristics of Dysarthric Speech Associated with Neurologic Disease
Z01 NS 02185-07 CDP 55

The Characteristics and Treatment of Vocal Tics and Language Processing in Gilles de la Tourette Syndrome
Z01 NS 02247-05 CDP 58

Cis Platinum and Early Identification of Ototoxicity
Z01 NS 02336-04 CDP 61

The Effects of Stimulants on the Auditory Processing and Language Skills of Hyperactive, Language Impaired and Normal Subjects
Z01 NS 02337-04 CDP 63

Analysis of Fluctuating Hearing Loss Associated with Cogan's Syndrome
Z01 NS 02395-03 CDP 66

Auditory Deficits in Osteogenesis Imperfecta
Z01 NS 02396-03 CDP 68

The Development of Acoustic Measurement Tools for Assessing Vocal Pathology
Z01 NS 02440-02 CDP 70

Hearing Assessment in Central Neurofibromatosis
Z01 NS 02441-02 CDP 73

Audiologic Findings in an Aging Population
Z01 NS 02470-01 CDP 75

Hearing and Neomycin Therapy for Type II Hyperlipidemia
Z01 NS 02471-01 CDP 77

Audiologic Findings in Autism
Z01 NS 02464-01 CDP 79

Hearing in Peripheral Neurofibromatosis
Z01 NS 02465-01 CDP 81

Pediatric Oncology Regime and Ototoxicity
Z01 NS 02466-01 CDP 83

Auditory Function and Cerebral Vasculitis
Z01 NS 02467-01 CDP 85

Audiologic Findings in Wegener's Granulomatosis
Z01 NS 02468-01 CDP 87

Small Cell Carcinoma and Hearing Loss
Z01 NS 02469-01 CDP 89

ANNUAL REPORT
October 1, 1980 through September 30, 1981
Communicative Disorders Program
National Institute of Neurological and
Communicative Disorders and Stroke

Introduction

The Communicative Disorders Program is concerned with the scientific bases of communication between individuals (speech, voice, hearing), with the scientific bases of the individual's communication with his or her environment (chemosenses, balance control) and with the disorders of those modes of communication. The normal physiology of many of these communication systems is poorly understood and, since in many if not all instances treatment or prevention of disorders is dependent upon a clear understanding of the normal, clinical management of disorders is often limited to symptomatic treatment or rehabilitation. The Program therefore encourages basic investigations of system physiology, and investigations directed to the application of basic knowledge in the prevention and treatment of disorders.

Communicative Disorders Program Staff

Ralph F. Naunton, M.D., Otolaryngologist, has served as Director of the Communicative Disorders Program during the past year.

J. Buckminster Ranney, Ph.D., has served as Deputy Director of the Program but was on leave of absence from January through May 1981 in order to attend a LEGIS Fellowship course.

Earleen Elkins, Ph.D., Audiologist, directs the hearing and vestibular portion of the Program and also supervises the Audiology Service at the Clinical Center, responsible for diagnostic clinical audiology and clinical research.

Christy L. Ludlow, Ph.D., Speech and Language Pathologist, directs the speech and language portions of the Program. In addition to her Extramural Activities, she maintains a clinical research program with the assistance of Ms. Celia Bassich, Research Speech Pathologist. Dr. Ludlow served for three months as Acting Deputy Program Director during Dr. Ranney's leave of absence.

Jack Pearl, Ph.D., Chemosensory Physiologist, is responsible for the chemosensory and haptic portions of the Program. He served as Acting Deputy Program Director for a two month period during Dr. Ranney's leave of absence.

Ernest Moore, Ph.D., Audiologist, was detailed to the Program during the early months of 1981; in July 1981 he accepted the position of Health Scientist Administrator (Audiology) with the Program on a permanent basis.

Jack Mahoney, M.D., Otolaryngologist, joined the Program staff as Health Scientist Administrator (Otolaryngology) in July.

Communicative Disorders Program Activities

Ad hoc Advisory Committee Meetings

The Advisors have met on two occasions during the past year. Each of the following was present at one or both of these meetings:

Dr. Robert C. Bilger
University of Illinois

Dr. Norman Geschwind
Beth Israel Hospital

Dr. Katherine S. Harris
Graduate School of University Center
of the City University of New York

Dr. Raymond D. Kent
Boys Town Institute

Dr. Robert I. Kohut
Bowman Gray School of Medicine

Dr. Murray B. Sachs
Johns Hopkins School of Medicine

Dr. David V. Smith
University of Wyoming

Dr. James B. Snow
University of Pennsylvania

Program staff also attended these meetings together with a number of other representatives from the Institute. The Advisors have provided direction to the Program bearing on future areas of research, in particular identifying those calling for special emphasis. They have also critically evaluated staff suggestions for new or special initiatives, approving of them or suggesting modifications. The next meeting is scheduled for October 1981.

Program Activities

In October 1980 in collaboration with the Office of Scientific and Health Reports a Summary Guide to the Programmatic Concerns of the Communicative Disorders Program was published together with a brief review of available support mechanisms. The guide has been invaluable in answering the many questions received from interested investigators concerning the possibilities of their securing research or training support. (Dr. Ludlow)

Tinnitus is an extremely common complaint, usually but not always associated with a hearing impairment. In an effort to encourage serious investigations of this hitherto largely neglected problem a Program Announcement on Tinnitus has been issued, encouraging the submission of grant applications in such areas as the measurement of tinnitus, tinnitus masking, development of an animal model for tinnitus, and the prevention and treatment of tinnitus. (Dr. Elkins)

Clinicians encountering patients with taste and smell disorders are commonly handicapped by a lack of expertise in measuring the senses of smell and taste despite the existence of these measurement methods in basic science laboratories. A Program Announcement has therefore been issued encouraging applications from clinicians for fellowships (individual or institutional) to secure training in laboratories providing this expertise. (Dr. Pearl)

In order to encourage physician involvement in research directed towards the prevention and treatment of otolaryngologic communicative disorders, a Program Announcement has been prepared encouraging the formation and application for support of Clinical Otolaryngologic Centers of Excellence. These would comprise clinical and basic scientists working in collaboration towards the prevention and treatment of specific disease entities. (Dr. Mahoney)

Recognizing the critical need in the speech and language fields for more well-trained clinical investigators, a Program Announcement has been issued encouraging applications for institutional training support for programs which will provide individuals interested in a research career in speech and language with clinical and laboratory research training in these areas (eg., neurolinguistics, neuropsychology, clinical neurophysiology, neuroanatomy, laryngology, psycholinguistics, speech science and speech perception). (Dr. Ludlow)

The Communicative Disorders Program information service has continued to improve user access to and understanding of the MEDLINE system of the National Library of Medicine. An evaluation study has been initiated to determine the effectiveness of the system from the viewpoints of clinicians and investigators in various specialties. Five MEDLINE centers in diverse geographic locations will take part in this study, more than 500 specialists in communication disorders having been registered so far. Information on the needs and bibliographic search practices of each of the user-participants has been collected, and is currently being analyzed by program staff in collaboration with the Office of Biometry and Field Studies. (Drs. Ludlow and Reiner)

Recognizing the importance of the genetic aspects of speech and language disorders, a conference on this subject has been conducted. Investigators with expertise in the area (including human and animal behavioral genetics, neuroanatomy, psychiatry, neurology, speech-language pathology, neuropsychology, dyslexia and statistics) participated. Each participant has prepared a paper on the subject of his or her presentation; these will form the substance of a monograph to be published in 1982. (Dr. Ludlow)

In collaboration with the Office of Scientific and Health Reports a brochure entitled, "Stuttering: Hope Through Research" was developed and published. This will provide information to the lay public on the disorders and type of treatment available. (Dr. Ludlow)

Staff Presentations at National and International Meetings

Elkins E, Pikus A. "Rehabilitative implications in Cogan's syndrome." American Auditory Society.

Elkins E, Pikus A. "Auditory anomalies in osteogenesis imperfecta." American Speech-Language-Hearing Association.

Ludlow CL, Cudahy E, Caine E, Brown GL, Bassich C. "Auditory processing deficits in the absence of a language disorder." Academy of Aphasia.

Ludlow CL, Brown GL, Cudahy E, Bassich C. "The differential effects of dextroamphetamine on auditory processing skills of normal-learning and learning-disabled boys." International Neuropsychological Society.

Ludlow CL, Caine E, Bassich C, Polinsky RJ. "Language performance of patients with Tourette syndrome." American Speech-Language-Hearing Association.

Ludlow CL, Bassich C, Brown GL, Ebert MH. "The effects of dextroamphetamine on language-impaired hyperactive boys." American Speech-Language-Hearing Association.

Ludlow CL, Polinsky RJ, Bassich C, Ebert MH. "Language and speech abnormalities in Tourette syndrome." First International Tourette Syndrome Symposium, New York.

Ludlow CL, Coulter D, Gentges F. "The differential sensitivity of measures of fundamental frequency perturbation to laryngeal neoplasms and neuropathologies." International Conference on Vocal Fold Physiology, Madison.

Naunton RF "The conservative use of tympanostomy tubes in the treatment of otitis media with effusion." The American Otological Society.

Naunton RF "Electrocochleography." National Symposium on Electrical Responses in the Auditory System, New York.

Naunton RF "Institute support for otolaryngologic communicative disorders research." Association of Academic Departments of Otolaryngology.

Naunton RF "Presbycusis." American Academy of Otolaryngology.

Naunton RF "Institute support for otolaryngologic communicative disorders research." American Council of Otolaryngology.

Pearl J "NIH support for research in the chemosenses." Association for Chemoreception Sciences.

Moore EJ, Williams A. "Peripheral and central auditory biophysical potentials in stutterers and non-stutterers." American Speech-Language-Hearing Association.

Staff Presentations at Other Meetings

Elkins E. "NIH support for research and training." North Carolina Agricultural and Technical University.

Elkins E, Shapiro J, Pikus A. "A study of osteogenesis imperfecta." Bethesda Naval Hospital.

Ludlow CL. "Gilles de la Tourette Syndrome." Howard University.

Ludlow CL. "Program and project planning." NIH STEP module, "Introduction to the Extramural Programs."

Ludlow CL. "The differential effects of stimulant drugs on perception, language and communication." Johns Hopkins University, Colloquium on developmental disabilities.

Ludlow CL. "Auditory processing disorders in hyperactive children and the effects of dextroamphetamine on auditory perception." Department of Hearing and Speech Sciences, University of Maryland.

Ludlow CL. Presented opening remarks (on behalf of Secretary Harris) at Congress of Logopedics and Phoniatrics, Washington, D.C.

Ludlow CL, Reiner B. "The use of MEDLINE for bibliographic searches in communicative disorders" (Demonstration). International Association of Logopedics and Phoniatrics, Washington, D.C.

Moore EJ. "Essentials of grant writing." Northern Illinois University.

Naunton RF. Key-note address. Better Hearing and Speech Month, Washington, D.C.

Reiner B. "Using MEDLINE for information retrieval in communication disorders." Department of Speech-Language Pathology and Audiology, Loyola College, Baltimore, Maryland.

Reiner B. "The MEDLINE evaluation project." Honolulu Medical Librarians Association.

Reiner B. "Speech sciences vocabulary and search techniques" (Workshop). Mid-Eastern Regional Medical Library Service.

Reiner B. "Use of MEDLINE for bibliographic searches in communicative disorders" (Demonstration). American Speech-Language-Hearing Association.

Other Staff Activities

Dr. Elkins:

- Served as Institute representative to the Committee on Hearing, Bioacoustics and Biomechanics (CHABA). (Member of Tinnitus working group.)
- Served as member, Committee on Speech Audiometry (Speech Discrimination) of American Speech-Language-Hearing Association.
- Addressed First Women's Bank of Maryland on Noise-Induced Hearing Loss.
- Served as member, advisory board for NASA/Gallaudet College project "Autocuer".
- Served as Equal Employment Opportunity committee chairman, (Hispanic, American Indian and handicapped persons).

Dr. Ludlow:

- Appointed Consultant to the Veterans Administration multidisciplinary study "Head-Injured Veterans from Vietnam", designing speech and language test procedures for the study in the assessment of dysarthria and aphasia.
- Edited the Proceedings of the Program-sponsored conference "The Assessment of Vocal Pathology;" this will be published as an "ASHA Report", thus bringing it to the 35,000 membership of the American Speech-Language-Hearing Association.
- Appointed Chairman of NIH Task Force to update NIH Project Officers Guide.
- Appointed American Speech-Language-Hearing Association representative to the American Association for the Advancement of Science.
- Appointed Associate Editor (Neuropathologies) for the Journal of Speech and Hearing Research.
- Elected Fellow in the International Academy for Research in Learning Disabilities.
- Served as member of Subcommittee for Education and Scientific Affairs, American Speech-Language-Hearing Association.
- Served as chairman, Committee on Scientific Affairs, American Speech-Language-Hearing Association.
- Served as chairman, Journal Selection Committee, Deafness Speech and Hearing Abstracts.
- Discussed research in speech and language supported by NIH, with the NINCDS Voluntary Health Agency Workshop.

- Invited to accept nomination as Vice-President, Education and Scientific Affairs, American Speech-Language-Hearing Association.

Dr. Moore:

- Served as Institute representative to the Committee on Hearing, Bioacoustics and Biomechanics (CHABA).

Dr. Naunton:

- Served as member, Committee on Hearing and Equilibrium, American Academy of Otolaryngology.

- Served as chairman, Membership and Credentials Committee, American Neurotology Society.

- Served as President, American Auditory Society.

- Served as American Academy of Otolaryngology representative to Joint Committee on Infant Hearing.

- Served as American Academy of Otolaryngology representative to American National Standards Institute (Bioacoustics).

- Served as member, ENT Device Section of the Dental, Ophthalmological and ENT Panel of the FDA.

Dr. Pearl:

- Taped radio program on Disorders of Taste and Smell.

Dr. Ranney:

- Served as member, Committee on the Clinical Fellowship Years, American Speech-Language-Hearing Association.

- Attended LEGIS Fellowship Seminar Series on Capitol Hill during the five months January through May 1981.

- Served as member, American Speech-Language-Hearing Association Task Force on Housing.

Dr. Reiner:

- Manned exhibit at ASHA Convention, demonstrating MEDLINE data base.

Clinical Activities

Clinical research in hearing, under the direction of Dr. Elkins and in cooperation with Ms. Pikus and Ms. Grimes of the Clinical Center, continues to focus on hearing losses associated with various diseases and disorders. Improved diagnosis and treatment remain the framework for twelve studies involving ototoxicity, aging, pediatric oncology, autism, peripheral and central neurofibromatosis, osteogenesis imperfecta and Wegener's granulomatosis. The successful treatment of sudden hearing loss in Cogan's Syndrome with corticosteroids has been documented in a publication in cooperation with the Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases. Physical relocation of the clinical facilities in the Clinical Center during late summer caused some delay in data collection. Details of the studies in progress may be found in the reports of research projects.

Clinical speech and language research has continued under the direction of Dr. Ludlow with the assistance of Ms. Bassich and in collaboration with intramural scientists in NINCDS and the National Institute of Mental Health.

Portable laboratory instrumentation for testing Clinical Center patients with laryngeal pathology has been developed, thus allowing real time recording of acoustic, laryngographic and accelerometric data on laryngeal function of patients. Determinations of the validity of phonatory assessment of laryngeal pathology and the efficacy of its treatment are proceeding. Several studies of neoplastic, neurologic, and functional laryngeal pathologies have been initiated.

The dedicated computer system used by the speech and language laboratory has been upgraded in several directions, including the provision of a fourfold increase of memory. This memory capacity permits processing vocal signals obtained simultaneously through acoustic, laryngographic, and accelerometric sensors in studies of laryngeal pathology.

A universal movement tranducer for sensing lip and jaw movement during connected speech on three directional planes has been completed in cooperation with Mr. Walker of the Biomedical Engineering Branch of the NIH. The device will be used in planned research on aberrations of lip and jaw movement during speech associated with tardive dyskinesia, dystonia, chorea and other involuntary movement disorders.

Several studies have been completed and the results submitted for publication. Major findings include the following:

(1) Vocal frequency perturbation is augmented in cases of laryngeal neoplasms but not by neuropathologies affecting laryngeal function; thus, perturbation measures can differentiate between disease processes regardless of the degree of hoarseness exhibited.

(2) There is a positive correlation between age and frequency perturbation over the age range 18 to 65 years in normal speakers.

(3) The precise effects on vocal functioning of brain stem lesions depended upon the locations of the pathologic changes. Thus lower motor neuron involvement resulted in increased diplophonia, - absent in instances of lesions confined to the basal nucleii.

(4) An expressive language dysfunction was found in all patients with Tourette syndrome. This pattern of dysfunction was found at all ages, was unrelated to the severity of the syndrome and is similar to the language symptoms associated with involvement of the supplementary motor area (transcortical motor aphasia).

(5) Symptoms of disordered speech production were identified which can accurately differentiate between patients with Shy Drager syndrome, those with Parkinson's disease and aging control subjects.

Staff Publications

Ludlow CL. Impaired language development: Hypotheses for research. Bulletin of the Orton Society 1980; 30: 153-69.

Ludlow CL. Recovery and rehabilitation of adult aphasic patients: Relevant research advances. In Reiber RW, ed. Communication Disorders. New York: Plenum Publishers Inc, 1981.

Rapoport JL, Buchsbaum MS, Weingartner H, Zahn T, Ludlow CL, Mikkelsen E. Dextroamphetamine: Cognitive and behavioral effects in normal and hyperactive children and normal adults. Archives of General Psychiatry 1980; 37: 933-43.

Caine ED, Polinsky RJ, Ludlow CL, Ebert MH, Nee LE. Heterogeneity and variability in Tourette syndrome. In Chase T, Friedhoff A, eds. Tourette Syndrome. Raven Press, New York, in press.

Caine E, Weingartner H, Ludlow CL, Cudahy E, Wehry S. Qualitative analysis of scopolamine induced amnesia. Psychopharmacologica, in press.

Ludlow CL, Hart MO. The assessment of vocal pathology. ASHA Reports, in press.

Ludlow CL. Directions for the development of improved methods for assessing vocal pathology. ASHA Reports, in press.

Ludlow CL, Polinsky RJ, Caine ED, Bassich C, Ebert MH. Language and speech abnormalities in Tourette Syndrome. In Chase T, Friedhoff A, eds. Tourette Syndrome, Raven Press, New York, in press.

Reiner BJ, Ludlow CL. Using MEDLINE for literature retrieval in communicative disorders. Asha Journal, in press.

Ludlow CL, Coulter D, Gentges F. The differential sensitivity of measures of fundamental frequency perturbation to laryngeal neoplasms and neuropathologies. In Bless D, Abbs J, eds. Vocal Fold Physiology. University of Wisconsin Press, in press.

Taste and Smell

Introduction

Taste and smell disorders reduce the quality of life and in severe forms can threaten life. Chemosensory disorders may be presenting symptoms of serious diseases and may contribute, because of inappropriate food preferences, to disease severity through malnutrition, obesity, diabetes, or hypertension. The recent establishment of clinical chemosensory research centers provides a multidisciplinary framework for the better prevention, diagnosis and treatment of chemosensory disorders.

Normal Structure and Function

Odors may be perceived through the olfactory or the trigeminal systems. If an irritating odor is perceived through the trigeminal system, anosmic subjects with respiratory or cardiovascular disease would be at risk. Electrophysiologic recordings from the olfactory and trigeminal nerves are being carried out in an effort to characterize the regional sensitivity of the mammalian olfactory mucous membrane to different odors; a specially constructed olfactometer delivers odors for precise periods of time and in precise concentrations. Phenyl ethyl alcohol produces little or no response from the trigeminal nerve in rats, suggesting that it is a pure olfactory stimulus; on the other hand, amyl acetate and butanol produce active responses from the trigeminal nerve.

The distribution of odor molecules across the nasal mucosa is being quantified according to physical-chemical variables, determining the ability of odor molecules to reach particular receptors; this will provide information on the mechanisms and abnormalities of odor analysis. Distribution patterns of odors on two areas of the nasal mucosa of frogs, the principal nasal cavity and the inferior nasal cavity (including the vomeronasal organ), were studied by means of radioisotope labelled molecules; the inferior nasal cavity received only a small percentage of the delivered molecules of octane and butanol but once sorbed into the mucous membrane they were retained for a longer period of time in the inferior cavity than in the principal nasal cavity.

Excitatory responses recorded from olfactory neurons have long latencies compared with those from other sensory receptors. The explanations of the long latency have been that there is either a delay in transduction or a delay in the access of the stimuli through the mucous layer to the receptor sites, which purportedly are near the point where the cilia extend from the dendrites. Recent results are consistent with an alternate explanation: the diffusion of the odorant through the mucous layer is rate limiting, the concentration of the odorant at the receptor site having to build up to a certain threshold to trigger a response.

Olfactory laterality was studied by comparing butanol sensitivity in both nostrils in nine left-handed and ten right-handed college students with a flow-dilution olfactometer. The sensitive nostril corresponded with that of handedness, particularly in the left-handed. Airway patency showed an inverse relationship to nasal sensitivity. Because 117 other subjects showed no relationship between handedness and airway patency, the latter cannot explain the observed relationship between handedness and nasal sensitivity.

A physiocochemical model of the transduction process for taste receptors is being established. The model for the receptor surface incorporates the action of variable surface charge, ion binding, and diffusion on the microenvironment of phospholipid monolayers and provides explanations of many chemosensory events. The model is consistent with reports that charged phospholipids affect salt and acid reception. In the model the changes in NaCl concentration induce changes in the surface pressure of charged phospholipids. Further, any ion effect is a composite of specific ion association and nonstoichiometric electrostatic events common to all ions. If surface pressure changes in the receptor membrane affect transduction, agents that specifically change the surface pressure could interfere with normal transduction. Because increases in the H^+ ion concentration and Ca^{++} ion concentration result in a decrease in the surface pressure, surface pressure decreases should be excitatory in taste reception and increases should be inhibitory. The model has been applied to previous results: (1) The water response in man and animals signifies that water has a sour-bitter taste following the adaptation of the tongue to solutions as salty as normal saliva. Local increase in acidity as NaCl is removed from the tongue appears to be involved in this water response. (2) The surface active properties of gymnemic acid were compared with those of a well-known surfactant, sodium lauryl sulfate, a detergent used in many toothpastes. The actions of the two agents were similar in both their ability to decrease surface tension and to penetrate easily the insoluble layers of phospholipids. Psychophysical results in people were consistent with the hypothesis that the surface activity may be a property common to a class of taste modifiers which includes the two agents tested. Other agents that perturb the free energy of surface membranes may prove to be taste modifiers. Responses to salt, sucrose, and quinine were suppressed by the taste modifiers. The taste modifiers decreased the perception of the intensity of the tastants by a constant percentage which was independent of the concentration of the tastants. Results do not rule out altogether a stoichiometric effect on receptor proteins. Because taste responses are suppressed for only several minutes after exposure to the surfactants, results are hard to interpret as a result of cell destruction. (3) Events occuring at the dorsal lingual epithelium after the arrival of the stimulus but before excitation of the taste nerves have been examined by means of a modified in vitro method, used for the first time in connection with taste. The tongues of freshly sacrificed dogs served as a remarkably stable preparation. Results showed that hypertonic NaCl solutions produce active ion transport across the dorsal surface of the taste epithelium but not nongustatory lingual tissue and proved that the metabolically-active epithelium is not necessarily a tissue of low permeability as has been supposed. The effect is an active process because the mucosal-serosal transport was abolished by the addition of quabain to the serosal side. When either sodium acetate or tetramethylammonium chloride was substituted for NaCl in the mucosal medium, the active currents decreased but their sum at a given concentration approximated that of NaCl at the same concentration. This near identity suggests that the current is made up of inward Na and outward Cl movement. Results suggest that active ion currents are crucial not only in the normal excitation of taste nerves but in the elicitation of electric taste by anodal potentials.

Single chorda tympani nerve fibers of rat and hamster were tested with six sugars. Fibers were preselected: they had to respond only to 1M sucrose or 1M maltose. Correlation analysis for each sugar gave the following results: In rat preparations, the number of impulses during the first five seconds of a sucrose response gave lower correlation values than those of other sugars. The analysis separated neural responses into three major groups: (1) sucrose, (2) NaCl and (3) fructose, maltose, glucose, galactose and lactose. In hamster preparations, sucrose again showed lower correlation values than other sugars. Results suggest that neural responses to sucrose differ significantly from those of other sugars. In rat, some single chorda tympani nerve fibers gave larger responses to maltose than to sucrose, while in hamster, nearly all fibers responded best to sucrose. The order of effectiveness of sugars was maltose, fructose, lactose, sucrose, glucose, and glactose in rat, and sucrose, fructose, galactose, glucose, maltose, and lactose in hamster. These electrophysiological responses of single chorda tympani nerve fibers to sugars agree with the behavioral sugar preferences found in rats by others. Maltase is a dominant sweet in rat; sucrose is a dominant sweet in hamster. That responses to sugars differ between species raises the possibility of different receptor sites for different sweets. The research could lead to good models for the study of the molecular properties of sweeteners and to the eventual design of compounds useful for diabetic patients. Another investigator is defining the three-dimensional structure of sweet proteins, such as monelline, with the method of x-ray diffraction.

Because of the health implications of the consumption of sweet and salty foods, interactions between taste and thermal sensations are of interest. Results of psychophysical studies of taste in college students are indicating that the intensity of the taste of sucrose is markedly influenced by temperature. For sucrose concentrations less than 0.4 molar, the stimuli warmer than mouth temperature were sweeter; greater than 0.4 molar, the cooler stimuli are sweeter. The effect of temperature on the tastes of saccharine and fructose was less than that on sucrose. The bitterness of quinine hydrochloride was affected by temperature in a complex way depending on the concentration of quinine. Temperature had little effect on the tastes of salt and citric acid. Results suggest that temperature changes may induce chemical changes in molecules like sucrose.

Abnormal Structure and Function

There is a lack of histopathologic information on the olfactory mucosa of patients with olfactory disorders, and on the ultrastructure of the cells in the basement membrane which generate into new olfactory receptors. Although biopsies have been taken from humans, they were probably respiratory rather than olfactory epithelium. A biopsy tool was developed to permit removal of a tiny amount of olfactory mucosa. A special biopsy knife was fitted on the tip of a small tube with a lens and carefully passed through the 1.5 mm crevice between the nasal septum and superior turbinate. With this tool olfactory mucosa has been taken from living patients.

People can lose their sense of smell following injury to the olfactory nerve from fracture of the cribriform plate. The anosmia, in part determined by scar formation, is not necessarily permanent. Studies have shown that sensory neurons in the olfactory epithelium of animals, including primates, can regenerate. Section at the fila olfactoria of the olfactory nerve in squirrel monkey induces rapid regeneration of the sensory axon terminals in the olfactory bulb glomeruli of the brain. A population of axons, from newly formed sensory neurons in the olfactory neuroepithelium, regrows, passes the cribriform plate and, on reaching the olfactory bulb, reinnervates the glomeruli. A new set of synaptic contacts is made between the sensory terminals and the post-synaptic dentritic processes of the glomeruli. In mice, the olfactory sensory neurons can be reformed from the stem cells even after total bulbectomy and their sensory axons can regrow in the spared portions of the forebrain where they form glomeruli and make synaptic contacts with the local neurons. The olfactory neurons maintain a normal turnover rate and in the neuroepithelium the olfactory marker protein has normal values. The presence of the olfactory bulb does not seem to be essential for the maintenance and maturation of a normal population of olfactory sensory neurons. When the axons fail to reach the central nervous system because of the formation of a dam of scar tissue, large neuromas form on the intracranial side of the cribriform plate. Though the olfactory sensory neurons survive, their turnover accelerates. Only 10% of these neurons are able to make olfactory marker protein.

There are no standard practical quantitative olfactory tests for use in clinical diagnosis and treatment of olfactory disorders. Scratch and sniff cards, embodying microencapsulated odors, have been used on a group of anosmic patients and normal students in an effort to develop a clinically valuable test instrument. The patients identified odors only at the level of chance; normal subjects identified most odors correctly, the women outperforming the men. In an effort to develop a repository of information on patients with disorders of taste or smell, a questionnaire has been developed and so far used on fifty patients. It is noteworthy that more than fifty percent of subjects with total anosmia are smokers. The data derived from this questionnaire will be correlated with psychophysical data on taste and smell abilities and with data on physical and laboratory examinations.

The intensity of six different concentration of glucose and six of fructose were assessed by a method of magnitude estimation by college students, some with a positive family history and others with a negative family history for insulin-independent diabetes. The probability of the inheritance of a glucose intolerence in students with a positive family history was calculated with a model of simple recessive inheritance. The mean log response of the students to glucose was subtracted from that to fructose. A difference in these means of less than about 0.1 was shown by many of the students with a positive history but by none of the students with a negative family history. This observation suggests that there is a specific taste defect in glucose recognition in insulin-independent diabetes that may serve as a genetic marker.

Touch

Introduction

There is interest in using touch as a communication channel for the deaf-blind. To help understand the cababilities and limitations of touch as a communication channel, various vibrotactile patterns have been applied to the skin. Two ways of applying the patterns to the skin are in sequential parts (scanned mode) and in all or none wholes (static mode). The Optacon (optical-to-tactile conversion) instrument, intended as a reading aid for the blind, presents vibrotactile patterns to the finger in the static or the scanned mode.

Normal Structure and Function

Basic research can provide a rationale basis for the use of touch as a communicative channel. People have remarkably low detection thresholds of about 6μm for the texture perception of height when they stroke tiny bumps with the middle finger. Stroking the skin with a textured surface may be a more natural way to stimulate the skin than poking the skin with a pointed object. To address this possibility a tactile stimulator is being built which can rub the skin with a multitextured wheel and measure horizontal and vertical displacement of the skin. Such measurements are important for stimulus control and reproducibility, and it may eventually be possible to have textures that provide signals to only one class of skin receptors and random noise to all others. That would be a practical alternative to calibrated horse hairs and two-point threshold tests of touch.

A psychophysical matching procedure was used to measure the effect of a conditioning stimulus on the enhancement and suppression of vibrotactile sensation magnitude of a test stimulus which was applied to either the ball of the thumb or the middle finger. The conditioning stimulus was presented either before or after the test stimulus. The stimuli were 20 msec bursts of sinusoids at frequencies of 25 and 300Hz. The 300Hz frequency is in the sensitivity range of the Pacinian vibrotactile channel which probably summates energy over time and space. The 25Hz frequency is in the non-Pacinian channel which shows neither spatial nor temporal summation. When the test and conditioning stimuli were on the same site, both forward and backward enhancement effects were observed. When the two stimuli were presented to different sites, the sensation magnitude of the test stimulus was suppressed at short interstimulus time intervals. At longer time intervals, enhancement was observed only in the forward direction. The same psychophysical matching procedure was used to measure the effect of a conditioning stimulus presented to a contralateral site. When both stimuli were presented to the thumb of the same hand, the conditioning stimulus enhanced the sensation magnitude of the test stimulus at time intervals of up to 400 msec. Enhancement was also observed when the test stimulus was on the thumb and the conditioning stimulus was on the contralateral thumb, the ipsilateral middle finger, or the contralateral middle finger. When the conditioning and test stimuli were applied to separate sites, enhancement was maximal when the stimuli were 150 msec apart. At intervals of less than 100 msec, suppression was observed. Enhancement and suppression were observed only when the frequencies of the two stimuli were within the same vibrotactile information-processing channel. In other experiments the effects of a masking stimulus applied to the ball of thumb were measured at the pad of the index finger to examine the effects of multiple-site stimulation and the effects of masking across vibrotactile channels. Results indicate that masking takes place between sites and appears to be effective across channels. However, careful measurements of the cross-channel masking showed that these effects are due to the spread of high-intensity vibrations between the two sites. These experiments are continuing because the cross-channel masking noted by other researchers is probably dependent on the use of high intensities that excite more than one mechanoreceptor system.

Interactions between temperature and touch may provide added information to the deaf-blind. Tactile acuity was studied in normal college students with two-edge thresholds as a function of stimulator temperature. Both warming and cooling improved tactile acuity 40% which was statistically significant. The improvment seems to be the result of temperature acting directly on mechanoreceptors, as pure thermal sensations alone have virtually no spacial acuity.

Abnormal Structure and Function

The effects of static and scanned modes on performance were compared in parametric studies with the Optacon in normal college students. Static application was advantageous until the letters were made very small and advantageous at durations less than 200 msec. That good letter recognition with the static mode was still possible at a duration of 4 msec is important because of the opportunity to present comprehensible information very rapidly. Letter recognition with the static mode was dependent on voltage, which affects perceived intensity of the letters presented, whereas voltage had little effect on letter recognition with the scanned mode. Both modes of pattern application produced similar results with masking that was produced by activating certain of the top rows of the vibrotactile pins. Masking after the letter came on produced more interference than forward masking. Even the backward masking did not produce much interference when presented more than 150 msec after the letter.

Structure and Function

Knowledge of the function of the auditory system is the result of individual and cooperative efforts of numerous investigators. From a study encompassing work from the ear canal to the eighth nerve, modelling of the cochlea has provided information on perilymph velocity, the resonant ability of the tectorial membrane and stereocilia systems, the non-linearity of basilar membrane vibration, and the shearing motion between the tectorial membrane and the reticular lamina. The results of physiological tuning curve (TC) data indicate that extracellular TCs obtained from Inner Hair Cells (IHC) appear as sharp as neural TCs obtained at the same characteristic frequency in the same animal species. Intracellular TCs tend to be less sharp, perhaps due to injury. An intriguing finding is that potentials recorded in response to sound bursts in supporting cells are larger than those recorded extracellularly.

The study of transduction processes in the hair-cell organs of the auditory system has included analyses of the mechanical, electrical, synaptic and neural function. One investigator's work does not support a wide-held theory that basilar papilla of the alligator lizard are tonotopically organized by frequency. Rather, it is felt that no spatial dependence is apparent and the entire papilla moves in phase over a range of frequencies of sound from 0.5 to 4 kHz.

The examination of inner ears of various species contributes to a general understanding of the auditory system. For example an investigator is looking at the mechanisms by which relatively simply organized vertebrate auditory systems process acoustic information. He reports that these animals discriminate sound stimuli on the basis of temporal cues only and, unlike mammals, do not use spectral cues. This comparative work shows that inter-spike intervals in eighth nerve fibers carry information about the acoustic waveform and that auditory analysis by the central nervous system (CNS) appears to involve time-interval measurements.

Mechanical models of the peripheral auditory mechanisms have evolved from physiological studies of the cat and chinchilla. Current explorations with these models indicate that non-linear distortion products observed near the eardrum are not a function of the ear canal but are probably generated in the primary-frequency region of the cochlea. Experiments employing temporary fatigue, cyanide poisoning and anoxia show that this distortion-product generation requires normal physiological processes in the cochlear sensory apparatus.

Another study, employing the cat as an animal model, is detailing the manner in which components of multiple-frequency or complex tones interact to produce responses in single auditory nerve fibers. The methodology includes quantitative analyses of the "two-tone suppression" phenomenon and of the behavior of discharge synchronization to low-frequency tones. This investigator has found that suppression of discharge synchronization behaves in the same manner as suppression of discharge rate. Similarly, suppression exists throughout an auditory nerve fiber's response area and suppression magnitude is determined exclusively by the frequency and intensity of the suppressor tone. Interestingly, the suppressive effect of a given tone is not correlated with its ability to excite nerve fiber response.

The cochlear nucleus of the chinchilla is being examined to identify the neurotransmitter at acoustic synapses and determine the effects of putative amino acid transmitters on coding properties of auditory neurons. These data suggest that aspartate or a substance with an affinity for the aspartate receptor may be the acoustic nerve transmitter. By understanding the neuropharmacology of synaptic mechanisms giving rise to the area-specific response patterns of the cochlear nucleus neurons, it is hoped that we may understand communicative disorders of auditory processing which occur beyond the peripheral mechanism. The cochlear nucleus cells of the cat are being explored to determine the neural generators for some of the component waves resulting from acoustic evoked responses to click stimuli. Bilateral, ipsilateral and contralateral innervations appear to be either primary or secondary contributors to each component wave.

Other work with the same animal model is detailing synaptic organization in the dorsal cochlear nucleus and lateral lemniscus. This investigator is identifying difference in parent cochlear fibers as they enter the cochlear nucleus and is tracing connections from the cochlea by studying giant cells of the deep dorsal cochlear nucleus whose axons might send collaterals into the posterior ventral cochlear nucleus. She feels that since all small cell types in the deep dorsal cochlear nucleus are contacted by primary fibers, they are involved in the direct processing of auditory input. It is expected that these results may help define small CNS sites responsible for binaural interactions as well as the recognition of one tone among several or even temporal differences among sound stimuli.

One area of particular interest in understanding the auditory system as a source of sensory input, is in the localization of sound. Binaural hearing is essential for establishment of spatial awareness and location in space; thus one investigator found that by occluding either ear he could shift the locations of auditory fields. It appears that these fields derive from central integration of binaural inputs and that interaural intensities dictate the locations and boundaries of these fields. Additional binaural investigations are being supported at the single neuron level by studying potentials evoked in the auditory cortex as a result of electrical stimulation of the mesencephalic reticular formation. Analogous work in the visual system prompted these studies using binaural stimuli to examine excitatory and inhibitory processes in the auditory system. However, not all localization studies are limited to binaural input. One researcher is questioning the long-held theory that binaural time and intensity differences in auditory stimulation are the only cues for directional hearing. He has evidence from monaural studies suggesting that the pinna, by affecting the relative amplification of sound stimuli, contributes to the apparent location of narrow bands of noise differing in their frequency composition.

In addition, studies are underway that should improve our understanding of the normal process of speech encoding by the auditory system so that successful schemes can be developed for use with neural prostheses. Other investigators are seeking to understand the development of both normal and abnormal inner ears with the expectation that such knowledge can be applied to the study of congenital deafness, whether caused by genetic or acquired factors. Similar work has already produced a small but important clinical tool for the management of congenitally deaf children. It has been shown that the brainstem is an inducer of normal membranous labyrinth development and that the periotic mesenchyme tissue surrounding the developing membranous labyrinth has an inductive role in the development of the sensory structures in the membranous labyrinth. Therefore, if the brainstem or periotic mesenchyme has a defect, then it may be suspected that the membranous and bony labyrinth may also be congenitally malformed. The reverse, abnormal labyrinth related to abnormal brainstem, is also suspect and can be easily determined by x-ray and careful examination for central nervous system malformation or malfunction because of the possible inductive factor between the brainstem and developing inner ear.

A number of investigators are concerned with the ototoxic effects of noise- and drug-exposure. By controlling the damaging doses, one group of researchers is evaluating the damage to the organ of Corti of animal models and relating these findings to behavioral responses of the animals. After both types of exposure, noise and a combination of kanamycin and bumetanide, comparisons were made of audiograms; whole-nerve action potentials; locus of tips of individual nerve-fiber tuning curves; the weakest intensity that would produce a response in any of the 100-150 nerve fibers tested; and, a chart showing hair-cell destruction as a function of position along the basilar membrane for each animal. They found that the tips-of-tuning curve data were related to the pattern of hair-cell loss. The other three estimates of threshold agreed reasonably well with each other but did not reflect the rather large areas of destroyed hair-cells shown in the cytocochleograms. Detailed exploration of hair-cell damage and amount of noise-exposure indicates that the relationship holds up well over a considerable range of exposures. For example, 0.15 days of exposure at 112 dB SPL produces essentially the same average permanent threshold shift of 15-20 dB and hair-cell destruction of 10% as 1.5 days at 102 dB of noise, 15 days at 92 dB of noise, or 150 days of 82 dB of noise. When the sound pressure level of the noise exceeds 115 dB, the increased damage at this particular exposure level suggests that the mechanism responsible for the damage shifts from primarily biochemical to primarily structural. These results have now prompted the investigators to study the "critical intensity" region in more detail by looking at breaks in the basilar membrane that permit mixing of endolymph and perilymph.

The augmented ototoxicity of certain combinations of drugs is also under study in animal models. By using non-aminoglycoside antibiotics or the cancer chemotherapeutic drug, cisplatin, in combination with four loop-inhibiting diuretics, it has been shown that the diuretic potency does not correlate with ototoxic interaction potency. This investigator also found that the interaction of kanamycin and ethacrynic acid produced more rapid and continuing swelling of the stria vascularis than did either drug with saline or saline alone. Human ototoxicity is being studied by electron microscopic examination of temporal bones from patients with documented exposure to loop diuretics. Indications of marked intercellular edema of stria vascularis and the dark cell area of the vestibular system are worthy of note in this preliminary work.

Another morphological study of the inner ear is seeking to understand the peripheral auditory nervous system and shows that nerve fibers frequently synapse with some of the spiral ganglion cells. These synaptic fibers were all unmyelinated and remained small in size. It is felt that a group of neurons are under the influence of nerve fibers coming from the brainstem and thus may indicate that hearing is constantly monitored or even regulated by the autonomic nervous system. This same investigator is attempting to learn more about Meniere's disease, a disease associated with the typical symptoms of hearing loss, vertigo and tinnitus. He found that Meniere's disease did not greatly modify the potassium permeability of the endolymph-perilymph barrier in the cochlea.

Psychoacoustics

The study of psychoacoustics provides us with knowledge of how the auditory system processes a variety of sound stimuli. Ideally, one would like to correlate perceptual responses to specific findings of the physiology or neurophysiology of the system but the science is far from attaining this goal at the present time. However, many investigators are seeking to understand auditory processing by altering the parameters of the input signal and measuring the output response by various procedures. Development of clinical tests for the differential diagnosis of hearing impairments is the ultimate goal of these psychoacoustic studies. Frequency discrimination is under investigation by comparing psychophysical tuning from a population of listeners with normal hearing and those with sensorineural losses. The results indicate that when impaired subjects have a 40 dB or greater loss of sensitivity identified as cochlear in origin, they display abnormally wide tuning curves. The probe frequencies used were 0.3, 1.0, and 3.0 kHz. Similar findings emerged from a study measuring time constant responses on the same impaired subjects. The investigator interprets these findings to indicate that the rate of recovery from sensory excitation is slower in these patients at frequencies of their loss of sensitivity than it is in normal-hearing subjects.

Other work comparing normal listeners and subjects with bilaterally symmetrical noise induced hearing loss is exploring binaural phenomena via interaural intensity differences; it is found that these patients show about a 6 dB reduction in release from masking than do the normal-hearing subjects. It is postulated that the processing of interaural intensity differences occurs in the region of the lateral superior olivary complex. Noise induced hearing loss patients are subjects in another study where the investigator reports that they show a marked loss in loudness perception at both the frequency of the exposure and at a frequency one-half octave above it. He feels that this indicates a partial dissociation of threshold and supra-threshold measures of after-effects of exposure to intense sound. These findings may support a theory of basilar membrane mechanics which states that the maximum of the traveling wave envelope moves basally as a function of intensity.

Another study of binaural phenomena is relating auditory theory with psychoacoustic data to reveal how the human separately and simultaneously localizes different types of sounds in a noisy environment. For example, when normal listeners perceive a diotic 0.5 kHz target signal, the lateral position of the image is displaced just as much by a monaural masker of 4.1 - 5 kHz as it is by a similar masker of 0.1 - 1 kHz. Measures of interaural time and intensity differences are felt to be effective means of indicating perceived location of the sound source. Such alteration of the ordinary binaural listening situation is commonly referred to as lateralization.

Investigations of normal-hearing subjects' responses to various sound parameters continue to increase our knowledge of normal auditory processing. Currently, one investigator seeks to determine whether normal listerers code the pitch of sounds by temporal or tonotopic means. One study using a temporal model shows that complex tones, with partials separated by equal ratios, behave as if they were octave intervals. Pitch-intensity functions are also being compared with intensity varied masking-patterns.

Treatment and Management of Hearing Impairment

The most widely used sensory aid for both adults and children is the conventional hearing aid. Maximum use of residual hearing is the ultimate goal; but this presents a continuing problem for the clinician who attempts to prescribe a hearing aid for the individual patient. The electroacoustic characteristics of hearing aids vary significantly and must be individually evaluated to find the optimum combination for each patient. This is the subject of a study currently in progress, in which investigators are employing objective performance measures comprising single syllables, sentences and paragraph selections of speech. Preliminary results are promising with as many as six variable frequency-response settings; but a feasible clinical procedure is not expected for several years. Another investigator, employing a different methodology, is finding that impaired listeners are successful in reliably ranking the instruments with which they perform best. However, the large number of uncontrollable variables inherent in commercial hearing aids make identifying differences among aids quite difficult.

Besides varying the frequency-response of hearing aids, some investigators are altering the amplitude of the signal. One group of investigators studied amplitude distributions for unprocessed and compressed speech materials to analyze the behavior of multichannel compression systems. Since compression is a non-linear process with memory, such systems are defined in terms of their response to simple static and dynamic stimuli. The results showed that the static compression ratio only applies to components of the speech envelope that vary on a syllabic time scale. Similarly, an evaluation of multiband limiting, designed to protect hearing-impaired listeners from high level speech and environmental sounds, shows that subjects with flat sensorineural hearing losses choose an overall listening level consistent with both maximum intelligibility over the range of input levels and long-term listening comfort. The results indicate that both higher average presentation levels and increased speech intelligibility scores are associated with compression limiting relative to linear amplification.

One possible solution to the problem of almost total sensory deafness (cochlear) is to bypass non-functioning cochlear hair cells and directly stimulate remaining auditory nerve fibers. If one can then provide the necessary frequency specificity, using a device that is small and flexible and that contains a sufficient number of channels necessary for speech, a major means of treatment for certain types of deafness may result. One effort to attain this goal is now being conducted, utilizing the combined efforts of an otologic surgeon, physiologist and electrical engineer specializing in printed circuit development.

On the other hand, work is still in process on rigid modular electrode arrays. They are fabricated using photolithographic techniques and utilize a sapphire carrier for mechanical strength and for inter-electrode insulation. Thus problems with insulation and inter-layer adhesions have been partially solved. Electrode durability tests in vitro and in vivo continue. In addition, experimentation proceeds on an eight-channel implantable receiver-stimulator contained on four custom integrated circuits. A computer-managed subject test facility used for psychoacoustic and speech comprehension studies are an integral part of the research program.

It is of importance to continue the evaluation of certain basic biological and physical factors related to the long-term use of the cochlear prosthesis. Systematic psychoacoustic, neurophysiological, behavioral and histological data on hearing capacity that obtains as a result of either the scala tympani or modiolar electrode are accumulating. Studies of such side effects of implantation as vestibular stimulation have been completed. Extensive data on thresholds, dynamic range, electrode impedance, and on electrical current spread in close proximity to the scala tympani have been obtained. Hearing performance and histopathological changes have been documented.

Work also continues on multichannel cochlear nerve stimulators. One investigator is constructing second-generation multichannel devices, with particular emphasis on the surgical disconnect plug, the transcutaneous transmitter receiver system, a sound processor-electrical stimulator, and percutaneous plugs and cables. Implantations in humans are on schedule.

Aural rehabilitative procedures are being developed and evaluated for persons with profound hearing loss who use a hearing aid or cochlear implant prosthesis. A test battery of Minimal Auditory Capabilities has been developed which, in addition to measuring speech recognition abilities, also measures recognition of everyday environmental sounds and lipreading ability. The test battery is a vehicle for comparison of hearing aid users and cochlear implant patients and for providing a measure of pre- and post-implant performance for profoundly impaired patients. Another study, which evaluated the psychological profiles of severely hearing-impaired patients, contradicts conventional thought that profoundly postlingually hearing-impaired patients suffer significant depression and paranoia. Measures to evaluate communication skills of congenitally deaf children is the subject of another investigation which shows that youngsters have a tendency to perform better with American Sign Language than with a conventional English grammar approach to language. It is important to note that these results are significantly age-related.

In order to develop and prescribe effective hearing prostheses, it is necessary to determine how speech is perceived by the hearing-impaired. A study designed with this objective in mind, using synthetic speech stimuli, shows that impaired listeners have more difficulty than normal listeners in providing correct responses to final consonants of words that are distinguishable by the voicing feature as in "cap" versus "cab." Significant work is underway to establish the effects of room acoustics, on the perception of speech by elderly hearing-impaired patients who report particular difficulty in highly reverberant conditions; the results show that these subjects have significantly more errors on final consonants in both reverberant and competing noise conditions.

An alternate mode of providing speech communication for the severely hearing-impaired patient is through the modality of touch. One approach has been based on the experiences of Helen Keller where the impaired "listener" receives speech information by placing his hand on the talker's face and concurrently monitors the movements associated with the speech articulation process. With a selected number of deaf-blind subjects as well as laboratory-trained subjects, measures of grammatical structure, contextual information and segmental level perception of vowels are being evaluated. These measures may also be of use in evaluating tactile speech communication systems that employ artificial devices.

Vestibular

Grant activity under the sub-program of vestibular function and equilibrium comprises experimental studies in neuroanatomy, physiology and neurophysiology, biochemistry and behavior. Some investigators concentrate on the peripheral apparatus, while others focus their attention on central mechanisms. A small part of the grant program is directed toward the development of or refinement of clinical instrumentation and tests. It follows that the major focus of vestibular research is in basic research areas, while a much smaller portion can be classified as applied research. Several of the grants involve preventive approaches. Some representative studies are summarized below.

The aim of one category of endeavor is to determine arborization and synaptic patterns of premotor axons related to horizontal eye movements in the oculomotor nucleus. Another objective is the investigation of timing mechanisms of nystagmus with emphasis on mechanisms which terminate the slow phase and initiate the quick phase. A third goal is to study ocular counter-rolling in normal human subjects and in individuals with known labyrinthine lesions or specific vestibular dysfunction. The approach is both anatomical and physiological, and the experimental animal is the cat. The procedure is to examine pause neurons and their synaptic relations with premotor neurons in the pontine reticular formation and vestibular nuclei using horseradish peroxidase (HRP) tracer techniques. Evidence has accrued which lends support to the notion that pause neurons, or at least some portions of them, are inhibitory neurons. Looking at the disinhibition of pause neurons on premotor burst neurons, and perhaps excitatory activity from the vestibular nucleus, the former may terminate the slow phase while the latter may begin the quick phase of nystagmus. Continuation of these studies to investigate convergence of excitatory inputs on the same premotor neurons may reveal a better understanding of at least one aspect of the rhythmic generation of nystagmus. Combining physiological and anatomical approaches, records will be obtained from within the axons in the medial rectus motoneuron-part of the oculomotor nucleus. The axons are characterized in terms of response to horizontal rotation and electrical stimulation. The abbducens nuclei, as well as other sites, are then injected with HRP and axonal terminations are examined by light and electron microscopy. Work on ocular counterrolling has as its focus the development of a specific test for bilateral and unilateral utricular dysfunction.

Another investigator uses a hook electrode or a glass microelectrode to record primary vestibular afferent activity from the posterior semicircular canal of the toadfish. The efferent vestibular system is then electrically stimulated so as to assess ongoing spontaneous activity and naturally evoked activity of afferents of the posterior canal. The aim is to determine branching patterns of the axons of efferent neurons. Neurons can be found in the midline of the medulla (so identified by their antidromic action potentials) in response to stimulation of various peripheral canal nerves. It would appear that each canal is innervated by its own population of efferents. That is, efferent neurons could only be antidromically activated from one canal. As an adjunct to these studies, retrograde transport of HRP was used to confirm cell body location or origin of the efferent vestibular system. Several neurons were found at the midline below the floor of the fourth ventricle. They are spindle shaped with dendritic processes extending for considerable distances in both dorsal and ventral directions. Those innervating the posterior semicircular canal appear to have a dorsal location. Light microscopic observations indicated extensive dendritic trees, somewhat similar to mammalian neurons, extending to the surface of the brain in both dorsal and ventral directions. Following the course of attendant axons, the investigator found them crossing the midline and innervating the contralateral labyrinth. Lesion experiments in the nucleus containing efferent cell bodies are now in progress. These combined experiments seek to determine whether the action of efferent neurons is excitatory or inhibitory. While an unequivocal statement cannot be made at this time, there are at least two classes of effect, - excitation as well as inhibition. The investigators hypothesize that the efferent synapses are excitatory, but that there is a canal-canal system which provides for inhibition.

The biochemistry of the vestibular and auditory labyrinth continues to be of interest to only a few investigators. Nevertheless, attempts are being made to develop an animal model of diabetes so as to subsequently assess various biochemical agents that can be identified in inner ear fluids and tissues. The experimental model is the chinchilla. A multifaceted approach is used involving biochemical studies along with anatomical and neurophysiological studies. The primary goal is to delineate mechanisms that produce hearing loss in diabetes and to gain insight into possible biochemical strategies for restoring normal hearing. The biochemical studies involve examining electrolytes in perilymph, oxygen tension in cochlear fluids, glucose concentration in perilymph, sodium, potassium and calcium exchange time in body fluids, osmolarity of inner ear fluids and protein counts in inner ear fluids. The diabetic condition is induced by administration of streptozotocin. In gathering baseline data, the degree of beta cell destruction in pancreatic islets was assessed. It was observed that a certain degree of recovery occurs after initial destruction, and may explain elevated insulin levels of the diabetic condition (hyperglycemia and hypoinsulinemia) in serum two weeks after administration of streptozotocin. The functional integrity of the ear is dependent upon maintenance of constant ionic composition of inner ear fluids; the mechanisms underlying maintenance of the constant composition are not well-understood. Since the chemical composition of inner ear fluids is derived from blood, knowledge of the rate of transport of various chemical substances from blood into inner ear fluids is essential. Characterization of the blood-labyrinth barrier is proceeding, and will serve as a baseline indicator of the diabetic condition and the homeostasis of the labyrinth. Oxygen tension in the inner ear fluids has been measured and agrees with results reported in the literature. However, these investigators have obtained not only relative values but also absolute values for the oxygen tension in the guinea pig and the cat. These absolute values have been determined on the surface of the round window membrane, in the scala tympani and in the scala media of normal chinchillas and normal guinea pigs. Thickening of the capillary vessels in experimental diabetes is also noted. Histological studies tend to complement the physiological studies.

As a corollary to the biochemical and anatomical studies, neurophysiologic studies assessed auditory nerve action potentials. Increase of the suprathreshold response amplitude was observed. On the other hand, the AP thresholds were within normal range at several frequencies. Moreover, subsequent measurements of the endocochlear potential (EP) were found to be abnormally high. These findings have led the investigator to hypothesize that high serum glucose levels may lead to an increase in strial function prior to the occurrence of strial dysfunction (hypothetical overloading of the system). To confirm this suspicion, further testing using the AP and EP as electrophysiological markers will include not only long-term tests, but also the evaluation of animals with transitory elevation of serum glucose levels in order to confirm the accelerated strial functioning.

Instrumentation for clinical vestibular testing that emphasizes early diagnosis and treatment of vestibular disorders continues to be of interest. As such, the continued development and clinical evaluation of microcomputer-based instrumentation systems for vestibular function testing is of primary importance. The goal is to improve the accuracy of tests, reduce attendant labor involved in testing and standardize procedures used for such tests. A prototype instrument has been assembled and tested. It consists of a two microprocessor-based system. One microprocessor collects and analyzes electro-oculographic nystagmus data and presents a summary of that information to the operator. The other microprocessor controls the generation of several vestibular stimuli, such as a moving chair, an optokinetic device and caloric stimulators. The computer analyzes all data, emphasizing accuracy and reliability. The degree of acceptance of the device by clinicians is being explored. As an adjunct to the evaluative process, work has begun on a digitized manually annotated data base of the spectral content of normal and abnormal vestibular and oculomotor responses. Computer analysis is correlated with manual reading via a comparator program. A great deal of effort has gone into developing an algorithm which requires a minimum of operator intervention. This approach, however, presents a number of problems. For example, what features and/or parameters of the nystagmus waveform should be extracted; how does one compare computer estimates with detection of events derived by a concensus of manual readers; and how can one examine the effects of algorithm module changes affecting the overall program? The problem becomes more acute when the investigator is faced with multiple-channel data. Event-by-event comparison between "true readings" (manual readings of the records) and the computer generated and controlled algorithm continues. The labor intensive nature of this task permits only qualitative comparison leaving quantitative results unexplored. Since the computer analysis of electrocardiograms involves problems similar to those of nystagmus analysis, and since EKG algorithm development can generate a digital recording of the raw waveform and perform comparative analysis so as to classify different aspects of the waveform, the investigator is using the EKG model in order to generate quantitative results. He is also employing multidimensional parametric statistical methods to compare "truth" with program performance.

Speech and Language

Speech Articulation

The articulation of speech sounds both in normal and misarticulating children continues to be studied by several investigators. Acoustic characteristics of normal sounds and misarticulations are examined to determine whether the spectral shapes differ, thus indicating an abnormal method of sound production in speech misarticulations. For the /s/ sound, the spectral shape differs from normal in misarticulating children and adults. The same issue is being examined for the /r/ sound by another investigator with less conclusive results.

Children's misarticulations can be subgrouped on the basis of acoustic spectral characteristics. A longitudinal investigation has followed misarticulating children past the stage of spontaneous self-correction--six to seven years. Children falling into different subgroups on the basis of the acoustic characteristics of their /s/ productions, can have different outcomes when not receiving speech therapy; one group spontaneously self corrects while the misarticulations of the other persist. These findings have immediate practical value; clinicians will be able to select those children needing speech therapy without spending time with those who will spontaneously develop normal speech.

Speech Motor Control

Recently, research has burgeoned in examining speech production as a highly complex motor activity with segments programmed in chunks in rapid succession. Speech gestures may occur too rapidly to depend on auditory, kinesthetic or proprioceptive feedback.

Several investigators are studying how normal speakers accommodate to substantial changes in oral configuration while producing speech. Large bite blocks are placed between the teeth altering the jaw angle and palatal height. Both the articulatory gestures used and the acoustic spectrum of the resulting speech sounds, are examined to determine whether speech gestures are preprogrammed to meet particular motor movement patterns. The results demonstrated that close to normal acoustic patterns were produced as a result of marked articulatory compensation of vocal tract and tongue gestures. The same results were obtained in the absence of auditory feedback; normal subjects easily adapted to perturbations with binaural white noise masking. The same experiment was conducted with deaf speakers (1 adventiously and 2 congenital) with similar results confirming the conclusion that once speech production is learned the role of auditory feedback in speech articulatory compensation is minimal.

Speech Disorders

Research on dysarthria, the speech disturbances accompanying neuromotor diseases, is limited; only one investigative team is working in this area. Biofeedback of respiratory and intra-oral air pressure control has had partial success in spastic patients.

Another speech movement disorder is verbal apraxia, a disorder affecting speech programming resulting from brain lesions in the left hemisphere in the region of Broca's area. This disorder is of theoretical interest for demonstrating those cortical regions responsible for speech programming. With the bite block research paradigm, verbal apractic patients required an adaptation period to readjust their articulatory movements to compensate for structural perturbations. The results indicate a deficit either in ability to monitor initial articulatory positions or to adjust production.

Supported research on stuttering continues to be meager due to the limited number of well trained investigators in this field. One investigator is conducting a genetic study of familial trends in the occurrence of stuttering. Positive family histories occur in the large majority of cases. Current research is aimed at determining behavioral traits which may be particularly affected in those stutterers with a positive family history as well as their relatives. A genetic model has been proposed with a different threshold for expression in the two sexes.

Studies of the speech of the deaf are few and only in the initial stages. The types of speech production strategies used by the deaf are being studied to gain an understanding of the motor errors responsible for the characteristic patterns of speech in the deaf and hearing impaired. The production of speech one sound at a time is one of the major problems in deaf speech. Analysis by synthesis is one approach being used to better understand the speech errors made by deaf speakers.

Speech Perception

This area of research has grown rapidly in recent years. Several investigators are actively pursuing the identification of those aspects of the acoustic speech signal critical for accurate perception. Using vowels in syllables, one investigator found that the first or last 15 msec of the syllable is adequate for listener identification. Another group of investigators have proposed a theory of invariant acoustic properties claiming that a universal set of phonetic features are present in all natural languages, that these can be characterized by invariant properties derived directly from the acoustic signal, that the human perceptual mechanism is specifically tuned to extract these properties and that they form the primary perceptual attribute used in ongoing speech perception. To date, these investigators have demonstrated that for alveolar and labial stop consonants the onset frequency is critical for perception rather than the gross shape of the onset spectrum. This theory has far reaching consequences for understanding normal speech perception and for the development of hearing prostheses. Many investigators have demonstrated that other features of speech syllables which affect sound identification, are contextually dependent and are presumably learned by speakers of a language. These features may not be universal and may depend on the language learned.

Laryngeal Pathology

Research on the structural and functional characteristics of the human larynx has increased considerably in recent years. At present, the research of ten investigators covers a wide range of topics including neuroanatomy, animal models of phonation, computer models of phonation and the effects of structural and neurological alterations of phonatory function. Theories of the mechanism by which phonation is produced in the human larynx have significantly altered in recent years. The vocal folds are no longer conceived as elastic bands but rather as multilayered bodies with very different viscous and elastic properties in each of the layers. The outer layer or cover is mucous membrane consisting of squamous epithelium on the outside and of collagenous and elastic fibers on the inside. This distinct layered structure plays an important role in vibration. The mucus covering on the free edge rotates in both an anterior-posterior as well as a lateral direction during vibration. These new concepts of vocal fold vibration have resulted from high speed photographic studies of vibration in excised larynges. Different pathological conditions are simulated in this preparation by placing masses on the folds to simulate neoplastic disorders and by increasing or decreasing fold length to simulate changes in tension.

Neurobiology of Language

The left temporal lobe is larger than the right in humans. Other right-left brain asymetries have been found in areas involved in language functioning. Pigmentoarchitectonics are also being used to examine the cellular organization of brain regions associated with speech and language functioning. Significantly greater numbers of cells were found in the frontalis magnopyramidalis inferior on the left side. However, in the thalamus only the lateralis posterior nuclei have more cells on the left side. The brains of animals known to have behavioral asymmetries are currently being studied to determine whether neuroanatomical differences are related to functional asymmetries.

Research on possible differences in cerebral organization between right and left handers has been fruitful. One investigator has demonstrated significant maternal familial sinistrality in left-handed females. These individuals have inverted hand posture and response latencies to unilaterally presented stimuli different from those of right-handers.

Another investigator has identified a subcategory of individuals termed "pathological left-handers" who have a history of a unilateral left frontal focal lesion prior to two years of age and who differ from familial left-handers. The significance of familial left-handedness to brain organization underlying language is that these individuals have less initial severity of aphasia than right-handers and recovery following the onset of aphasia.

Adult Aphasia

Research in aphasia continues to examine differences between aphasic syndromes for the purpose of ascertaining the independent language functions and the brain regions with which impairment of each function can be associated.

Concepts of Broca's aphasia have been altered by the finding that syntactic deficits affect all aspects of language functioning in this syndrome including reading, writing, speaking and understanding. This cannot be viewed as a disorder primarily of language expression and expressive syntax in particular.

Research on language learning by aphasic patients is the essential first step towards developing new treatment approaches. The new work-learning skills of Broca's and fluent aphasics reveal at least two different processes required for learning a new word. Broca's aphasics were found to develop specific concepts regarding the meaning of a new word but were unaware of what form class it belonged to. On the other hand, fluent aphasics acquire information about a new word's form class but do not have a specific notion about the word's meaning.

Also important for the design of improved treatment procedures, is an understanding of the cognitive and perceptual skills of different types of aphasic patients. Basic to naming skills is the perception of stimulus set; for example, differentiating between types of "cups" and types of "bowls". The differentiation between two types of stimulus sets is essential to accurate naming behavior. A recent study reported that the naming problems of fluent aphasics may result from a disorganization of concepts requiring perceptually guided classification between objects.

Dyslexia

Studies of adults with acquired reading disorders following brain injury have demonstrated two separable reading processes. One involving the translation of graphemes into their phonological representation, is the more usual reading process and the one used in teaching reading. However, in the absence of intact phoneme-grapheme translation rules, some patients (with "deep dyslexia") seem able to comprehend written words with high imagery through direct access to semantic decoding on the basis of the orthographic shape. These findings, if replicated by others, could have profound effects on the teaching of reading to children who have difficulty learning phoneme-to-grapheme translation rules.

Developmental Language Disorders

Research on developmental language disorders in children continues to be limited although the number of new investigators has increased in the last year. Developmental language disorders frequently result from other cognitive and physical abnormalities present in young children such as mental retardation and congenital deafness However, a significant proportion of developmental language disorders are primary and referred to as specific language disorders. In such cases, the etiology is unknown. To better understand the language difficulties of such children, studies of the acquisition of lexical information are being conducted. At the one-word stage in language development some language disordered children can learn new words similar to normal children but at a slower rate. Of these children, one group learns words based on their nominative content while another depends on non-referential information. The former group were better able to learn new words; a referentially-based training program would be most successful with this subgroup. Further experimental studies will identify the subgroups within this population and their particular treatment needs.

One of the primary characteristics of infantile autism is disordered speech and language development which can range from no speech production or comprehension to excessive echolalia with disturbed speech prosody. One investigator has been studying the intonation and timing of speech production in autistic children. The results indicate that autistic children differ in their temporal organization of speech by producing speech in a serial fashion, one word at a time, and one word after another rather than in larger rhythmic chunks of meaningful phrases as normal children do. These results also suggest that autistic children use intensity characteristics and not frequency to convey intonation in their speech patterns and that deficits in the perception of frequency changes in speech may be related to their speech prosody disorders.

Sign Language Studies

Studies of American Sign Language are aimed at determining the universal characteristics of human language, its acquisition and essential components independent of language form (speech). One investigator is comparing the language-learning process for sign language in deaf children of deaf parents with that of hearing children learning English from hearing parents. Several remarkable similarities are seen, suggesting that the language acquisition process, in part, may depend on cognitive development rather than on the complexity of particular linguistic items. For example, at two years of age deaf signing children delete inflections when imitating sentences similar to speaking two year olds. However, other features of natural sign language acquisition differ from the acquisition of spoken language but are uniform across several deaf children with deaf parents. The findings will enable the authors to develop tests of sign language development for the congenitally deaf.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1980 through September 30, 1981

UNIVERSITY OF FLORIDA (N01-NS-5-2313)

Title: Study of Auditory Sensitivity in Young Children

Contractor's Project Director: Donald C. Teas, Ph.D.

Current Annual Level of Support: $0

Objectives: This contract was awarded to study auditory sensitivity in young children. The goal was to develop and evaluate a battery of tests which could be used to characterize the hearing sensitivity of young children not suspected of having hearing deficits and to examine the feasibility of using such a battery to assess the hearing of infants and young children who are suspected of/or at-risk for hearing dysfunction. Particular emphasis was placed on the developmental aspects of the hearing ability of this population.

Major Findings: Three measures were developed and evaluated with infants and young children. Auditory brainstem responses (ABR) were obtained for infants to broadband clicks with center frequencies of 500, 1000, 2000, 4000 and 8000 Hz and intensities of 20, 40 and 60 dB (above normal adult threshold). The results indicate that latency decreases occur until 20 weeks of age and remain fairly constant by 25 weeks. The mean latencies are the longest for 1000 Hz and the shortest for 8000 Hz. Blink inhibition by acoustic leadtone measures were developed for use with children aged 2 to 30 months. Results are being analyzed for responses to stimuli presented at 500, 2000 and 8000 Hz. The third measure was an adaptive behavioral procedure which employed a visual reinforcement paradigm for use with children under age three years. Test frequencies included 500, 2000 and 8000 Hz. For infants, mean thresholds showed little change between 10 and 18 months with minimal frequency effect. Mean thresholds for 6-month-olds were similar to those for the older infants at 500 and 2000 but were significantly poorer at 8000 Hz.

Significance to Biomedical Research and the Program of the Institute: Procedures were needed to assess hearing of young children who are incapable of providing conventional responses. A battery of tests to determine hearing sensitivity at different developmental stages is essential to the initiation of a habilitation program so that the acquisition of language and speech is not delayed.

Cooperating Units: None

Proposed Course: Data collection terminated in April 1981. Final analyses are being completed and a final report should be submitted by November 1981.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1980 through September 30, 1981

MINNEAPOLIS MEDICAL RESEARCH FOUNDATION, MINNEAPOLIS, MINNESOTA (N01-NS-7-2378)

Title: A Comprehensive Study of the Language Recovery Process in Adults with Aphasia Following a Cerebrovascular Accident

Contractor's Project Director: Alan B. Rubens, M.D.

Current Annual Level of Support: $224,078 (Forward funded in FY '80)

Objectives: The purpose of the research is to develop increased understanding of the neurophysiological and behavioral bases of the language recovery process in aphasic adults. Multidisciplinary studies will determine:

1. The relationship between outcome of aphasia and the size and location of brain pathology and neurophysiological activity in each hemisphere;

2. The relationship between changes in location and size of brain pathology and neurophysiological activity of either hemisphere, and degree of language recovery;

3. Whether cognition is associated with the degree of recovery from aphasia; and,

4. Whether verbal learning/memory deficits are associated with degree of recovery from aphasia.

Major Findings: A total of 42 patients have already completed or are in the process of completing their six month testing schedule, leaving 18 new patients to be recruited to complete the study. Significant advances have been made in quantifying the CT scans. Sagittal sections through the temporal lobes allow location of the lesion relative to the sylvian fissure. A new method of reconstruction of CT scans allows for comparison of the length of right and left sylvian fissures to determine brain assymmetries and their possible relationship with initial severity and degree of recovery from aphasia.

The verbal learning and memory studies have demonstrated significant deficits in aphasic patients both early and later in the recovery process. Different patterns appear in different aphasic syndromes demonstrating an independence of immediate memory function from long-term or semantic memory; the former being associated with posterior temporoparietal and supramarginal involvement and the latter associated with anterior temporal and frontotemporal cortical involvement.

Nonverbal cognition testing has indicated that for most aphasic patients all nonverbal cognitive skills are relatively spared when compared with language ability. However, the conceptually more difficult measures are rarely performed completely normally even by minimally impaired aphasic patients.

Significance to Biomedical Research and the Program of the Institute: Language recovery in aphasic adults is not well understood. In most cases recovery is rapid during the first nine weeks following the onset of symptoms. The size and location of brain lesions, regional blood flow, and physiological response of each hemisphere during verbal behavior will determine the association between dominant hemisphere status and level of recovery from aphasia. If recovery is not highly associated with changes in the left hemisphere, and the right hemisphere is found to be involved in verbal functioning, both the right and left hemispheres may be involved in language recovery following a CVA. The results will be useful for determining appropriate approaches for treatment.

Cooperation Units: University of Minneapolis Medical Center

Proposed Course: The contract has been extended an additional year to allow for testing the full number of subjects (60). The projected termination date is 3/31/83.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1981 through September 30, 1981

UNIVERSITY OF ILLINOIS (NO1-NS-7-2380)

Title: Evaluation of a Test of Speech Perception in Noise

Contractor's Project Director: Robert C. Bilger, Ph.D.

Current Annual Level of Support: $60,084

Objectives: The purpose of this contract was to conduct experimental work to determine the inter-list equivalency performance by signal-to-babble (S/B) functions and validity of the Speech Perception in Noise (SPIN) Test.

Major Findings: Comparisons were made of SPIN Test responses to Lo- and Hi-context stimuli with the perceptibility of other speech materials of differing difficulty. The results indicated that the difference in difficulty is relatively independent of degree of hearing loss, signal level of stimuli presentation and instrumental distortion. These findings are highly related to the validity of the SPIN Test materials. The direct observational study of communicative behaviors of hearing-impaired adults has shown that most failures result from a signal that was not loud enough; a signal that was heard but misunderstood; or a signal distorted by background noise. The observational study is being compared to the SPIN Test results to determine the validity and clinical applicability of this new measure.

Significance to Biomedical Research and the Program of the Institute: Assessment of supra-threshold speech perception in noise would provide a valuable tool for the practicing clinician in managing hearing-impaired patients. Hopefully, the SPIN Test may also be employed as a predictive measure of the degree of benefit that persons with acquired sensorineural hearing loss may appreciate from a properly selected hearing aid.

Cooperating Units: None

Proposed Course: Data collection was competed in August 1981. Additional work was added to the project in September 1980 and required the redigitization of the revised SPIN Test on a 300 megabyte disk. Data analyses and a final report are expected in December 1981 when the contract will be completed.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1980 through September 30, 1981

CHILDREN'S HOSPITAL OF PITTSBURGH (N01-NS-8-2384)

Title: Decongestant/Antihistamine Therapy for Otitis Media with Effusion (OME)

Contractor's Project Director: Charles D. Bluestone, M.D.

Current Annual Level of Support: $0 (Forward Funded)

Objectives: To determine if the widely-used combination of an antihistamine and a decongestant is effective in the treatment of otitis media with effusion.

Major Findings: Over 600 subjects have been enrolled in this double-blind clinical trial and the attrition rate is below that anticipated. The contractor has sufficient numbers for completion as scheduled in Fy '81.

Initial analysis of the data by the statistical team was performed and of interest is the apparent strong dependence of cure rate on the duration of OME. Overall cure rate of children with 0-3 week duration of OME is approximately 33% whereas the overall cure rate in children with OME duration of more than 8 weeks is approximately 15%. These data also suggest some dependence of cure on the age of the subject. Overall, the 6-12 years age group demonstrate a 23% cure rate and for the 2 younger age groups the cure rate is approximately 18%.

Significance to Biomedical Research and the Program of the Institute: Otitis media is the most common illness seen in the pediatrician's office and despite the routine use of decongestants and/or antihistamines we lack objective evidence of their effectiveness. Otitis media has been a targeted area of research by NINCDS and this work will provide important information on the treatment of otitis media.

Cooperating Units: None

Proposed Course: All analyses will be completed during FY '81 and a final report is expected shortly.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1980 through September 30, 1981

PRESIDENT AND FELLOWS HARVARD COLLEGE, CAMBRIDGE, MASSACHUSETTS (NO1-NS-8-2399)

Title: Laryngeal Carcinoma: Identification of High Risk Factors

Contractor's Project Director: Kenneth J. Rothman, M.D., P.H.

Current Annual Level of Support: $0

Objectives: To identify those individual health, environmental, and occupational factors which will delineate persons at high risk of laryngeal carcinoma in the United States today. The following objectives will be met:

1. An integration of data available on factors associated with a high risk of laryngeal carcinoma in the United States;

2. An examination of mortality, incidence data and time trends with significantly high rates of laryngeal cancer over the last 10 years; and,

3. Investigations of occupational factors and their relationship with laryngeal carcinoma.

Major Findings: Regional variations in laryngeal cancer mortality rates were analyzed. Mortality rates increased with urbanization, were greater in lower socioeconomic brackets and were positively correlated with regional alcoholic beverage sales. Rates were higher in counties with heavy concentrations of chemical and printing and with large shipyards in the 1940s.

Time trends for incidence of laryngeal cancer were examined for 1970-1978. Overall, the incidence did not increase substantially. For the years 1974-1978, an increase was more pronounced among those under 60 years of age, especially females. The largest increase in incidence rates for women, and to a lesser degree for men, was observed in the South, especially among the 25-59 age group.

A case-control study examined the possibility of interaction between alcohol and tobacco, two risk factors for laryngeal cancer. Moderate synergy was found between alcohol and tobacco increasing the risk of laryngeal cancer; exposure to both factors increased the risk about 50 percent more than the increase predicted if the effects of tobacco and alcohol were simply additive.

Significance to Biomedical Research and the Program of the Institute: The chances of survival following laryngeal carcinoma can be significantly enhanced with early treatment and the vocal mechanism may be spared when surgical intervention is not necessary. Screening programs are needed of persons at high risk of laryngeal cancer (such as industrial male workers who are heavy smokers and drinkers between 60 and 65 years of age). Before such programs can be initiated, a clearer understanding is needed of what factors could delineate persons at high risk for this disease. The final report of this project will indicate what further research is needed for delineating persons who are at high risk as well as what is currently known about the relative risk for this disease in various sections of the population.

Cooperating Units: The National Cancer Institute, Office of Biometry; Yale-New Haven Hospital; and, St. Raphael Hospital, New Haven Connecticut.

Proposed Course: Both Phase II and III of the research have been completed by the contractor; a case control study of the relationship between occupational histories and the occurrence of laryngeal carcinoma will be completed by December 1981.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1980 through September 30, 1981

UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL, NORTH CAROLINA (NO1-NS-9-2305)

Title: The Acquisition of Language and Communicative Skills by Speech and Sign in Infantile Autism

Contractor's Project Director: Thomas Layton, Ph.D.

Current Annual Level of Support: $254,000

Objectives: To conduct an experimental study of the development of communicative skills by autistic children when training involves only speech stimuli, only sign stimuli, speech and sign stimuli presented simultaneously, or speech and sign presented independently. The research will determine after six months of training which method of language training results in: greater expressive and receptive language skills; greater use of language skills for communication; and greater retention of language skills following training. The study will also determine whether autistic children evidence cross-modality transfer of information learned in speech or sign to the other modality; whether simultaneous presentation of stimuli in two different modalities interferes with learning; and whether autistic children show similar language learning difficulties in both the speech and sign modalities.

Major Findings: Over 20 children are currently in the language training program; six are being taught by speech alone, five by sign alone, four with alternating instruction between speech and sign, and six by speech and sign combined (total communication). No definite results are yet available since subjects are still undergoing training in each of the modalities. To date, regardless of training modality used, subjects who are echolalic are acquiring new words in both speech and sign at a faster rate than those without this symptom.

Subject acquisition is on schedule and the language trainers are performing with adequate administration reliability.

Significance to Biomedical Research and the Program of the Institute: Impaired speech and language development is common to all children with infantile autism although the degree of impairment varies among children. The etiology of these disorders is not known and the bases for these children's specific difficulties in learning language is not well understood. Some have proposed auditory and speech processing difficulties which could account for these impairments. Recently, there have been clinical reports of marked success with some of these children in learning language using signs or gestures and reports that once such children begin to use signs to communicate they may vocalize spontaneously and develop speech for communication more readily. This research will examine these issues experimentally and have significance for the development of improved speech and language training for autistic children.

Cooperating Units: None

Proposed Course: The work for Phase II will require two years. The final phase, involving data analysis and report writing, will run six months and should be complete in December 1982.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1980 through September 30, 1981

UNIVERSITY OF CALIFORNIA, SAN DIEGO (NO1-NS-9-2322)

Title: Evaluation of the Outcome of Preschool Impairment in Language Development

Contractor's Project Director: Paula Tallal, Ph.D.

Current Annual Level of Support: $279,000

Objectives: To determine, through a longitudinal intensive study, the outcome of preschool impairments in language development. In particular, the research will determine:

1. Whether the patterns of development of language, speech, listening and learning skills found in four year old language impaired children differ from those of normal children when both groups are examined annually between four and nine years of age;

2. Whether preschool children impaired in language development have greater difficulties in acquiring reading and writing skills than normal children at six, seven, eight and nine years of age;

3. Whether preschool children impaired in language development are impaired in their verbal learning, memory and scholastic achievement in comparison with normal children at five, six, seven, eight and nine years of age;

4. Whether certain familial and language, speech, listening and learning characteristics of language impaired children at four years of age, are predictive of their language, reading, writing and scholastic abilities at five, six, seven, eight and nine years of age.

Major Findings: In November 1980, a site visit was conducted to review the experimental language, neuropsychological and cognitive batteries developed for use in the longitudinal investigation. The site visit team concluded that although the tests developed were of high quality they were extensive in number and would result in too many variables for analysis given the number of subjects to be tested. Further pilot testing was recommended to determine which of the test items were valid for assessing specific aspects of language at each stage in normal development between two and eight years of age. Similar pilot testing was recommended for parts of the neuropsychological, verbal learning and memory and cognitive test batteries. Pilot data was also requested to examine retest reliability, learning effects and whether the tests could be administered to language impaired children between two and eight years of age.

Pilot testing of 70 normal children with ten children at each age level between two and eight years and 20 language impaired children similarly distributed resulted in a 30% reduction in the test battery and number of data points. Only test items which were developmental and test a specific hypothesis regarding language development in disordered children were included.

The testing in other cognitive areas was similarly reduced. The results of a second review was excellent and subject testing for the longitudinal study was initiated in September.

Significance to Biomedical Research and the Program of the Institute: The research will provide critically needed information for clinical treatment and planning for language disorders. It will be determined whether language impaired children differ from normal children in their language acquisition or whether they are simply delayed in their development of the normal sequence of language acquisition. Present treatment procedures are based on the normal language development process. It is likely that this is inappropriate but until information is obtained on language development in the language impaired population, more appropriate methods cannot be developed.

The research will determine whether preschool impairments in language development are precursors of difficulties in learning to read and write. The research will provide a detailed analysis of the types of difficulties these children have when learning to read. With improved understanding of the reading deficits of children who have a linguistic difficulty, remedial procedures for this segment of the reading disabled population can be improved.

Cooperating Units: Children's Hospital and Health Center, San Diego

Proposed Course: A contract was awarded for the first three years to include the developmental phase, subject selection and the first eighteen months of the longitudinal study. A Technical Merit Review site visit will be held in the third year to review the study procedures before extending the contract for the final four years of the study.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1981 through September 30, 1981

UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER (NO1-NS-0-2328)

Title: Efficacy of Adenoidectomy/Tympanostomy Tubes for Persistent Otitis Media with Effusuion

Contractor's Project Director: George A. Gates, M.D.

Current Annual Level of Support: $242,938

Objectives: The purpose of this contract is to conduct a controlled clinical study to determine the efficacy of adenoidectomy and tympanostomy tubes for the treatment of persistent otitis media with effusion. Children to be studied will be those whose treatment comprises myringotomy with or without the use of tympanostomy tubes, adenoidectomy, or a combination of all three modalities. A number of follow-up phases are included in the protocol, so as to determine the most effective treatment procedures for improvement in hearing capabilities and prevention of recurrent middle ear effusions.

Major Findings: The investigators have conducted a total of 492 screening evaluations, 57 complete evaluations, performed 34 surgical procedures, and completed 84 routine follow-up evaluations. A second interobserver reliability and validity study is continuing, computer and mathematical analysis of tympanometric data have been initiated, concomitant normalization of various tympanometric information has been completed, and biostatistical refinement continues.

Significance to Biomedical Research and the Program of the Institute: Middle ear effusions cause conductive hearing loss, and occur in approximately 68% of all children. As such, the conductive component interferes with auditory reception, which in turn may cause anatomical and speech abnormalities, and may interfere with the acquisition of language and cognitive skills. Since there exists confusion and substantial disagreement about the most efficacious treatment, it follows that a controlled experimental approach to assess various treatment protocols is in order. Otitis media is a target area of research for NINCDS.

Cooperating Units: Santa Rosa Medical Center, San Antonio, Texas 78285

Proposed Course: The contract was awarded for a five-year period, beginning February 1, 1980, and running to January 31, 1985. Due to the longitudinal nature of the study, it is expected that the full five years will be needed. A site visit has been scheduled for July 1981, in order to assess progress.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1980 through September 30, 1981

PURDUE UNIVERSITY (N01-NS-0-2329)

Title: Determination of Effects of Hearing Aid Amplification on Children

Contractor's Project Director: Carl A. Binnie, Ph.D.

Current Annual Level of Support: $101,057 (Forward funded in FY '80)

Objectives: To determine whether hearing aid amplification significantly affects the residual hearing of the groups of children under study and if a relative threshold shift (comparison of pure tone threshold shift over time between the aided and unaided ears) relates in a significant manner to: the electroacoustic characteristics of the hearing aid; the amount of hearing aid usage in hours per week and number of months and/or years; the degree of hearing loss when the aid was introduced; the earmold or coupling system used with the hearing aid; specific or nonspecific etiological information; and progressive hearing deterioration.

Major Findings: Test-retest reliability measures of pure tone air- and bone-conduction thresholds, speech reception thresholds, tympanograms and acoustic reflex thresholds have been completed on normal-hearing children, age 2 to 16 years. Baseline audiometric data has been obtained from 25 severely hearing-impaired children as well as acoustic impedance measures and electroacoustic measures of their hearing aids. The functional gain measures have been initiated after normative data was collected from the normal-hearing control subjects. Preliminary psychophysical tuning curve data with adult hearing-impaired subjects were obtained for maskers 35 msec in duration. A 10-minute exposure to the octave-band 1200-2400 Hz at 105 dB SPL did not significantly shift pure tone thresholds in these listeners in the 3000 Hz region. Comparison of these data with pure tone thresholds will follow. The auditory brainstem response (ABR) portion of the project is being initiated after special enclosures of aluminum were fabricated for the TDH-49 earphones to reduce the electrical artifact produced by the signals. Amplitude and latency values will be determined.

Significance to Biomedical Research and the Program of the Institute: The National Research Strategy identified the following Goal #67 which this project addresses. The special needs of the pediatric and aging populations should be considered from the viewpoint of sensory aids and habilitation/rehabilitation processes.

Cooperating Units: Indiana School for the Deaf; Indiana University School of Medicine; Home Hospital in Lafayette, Indiana; and St. Elizabeth Hospital in Lafayette, Indiana.

Proposed Course: Data will continue to be gathered within the various sections of the project to answer the questions identified in Objectives above. Completion is expected in March 1983.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1980 through September 30, 1981

SYRACUSE UNIVERSITY, SYRACUSE, NEW YORK (N01-NS-0-2331)

Title: Methods for Studying Phonatory and Articulatory Control in Young Children Who Stutter

Contractor's Project Director: Edward Conture, Ph.D.

Current Annual Level of Support: $200,000

Objectives:

1. To develop measurement techniques and testing procedures for assessing the speech production skills of young children between four and six years of age which are noninvasive, objective and reliable.

2. To determine which aspects of phonatory and articulatory control during speech production differ in fluent and stuttering children between four and six years of age.

Major Findings: Pilot testing of the experimental procedures with young stutterers of four years of age has been successful. The subjects tolerate the acoustic, laryngographic, respiratory and surface EMG instrumentation well. Only the strain gauge head held equipment for measuring the lip and jaw displacement has not been well accepted and is extremely time consuming.

A preliminary study was conducted of the temporal characteristics of fluent speech production of young stutterers and their normal fluent peers. Results of computer-assisted acoustic analysis of speech timing indicated that young stutterers have longer voice onset time, vowel duration and rate of formant transition during fluent speech than normal children. These findings support the notion that physiological disturbances are associated with all speech movements in young children who stutter.

A videographic study of young children who stutter has demonstrated four categories of non-speech oral, head and neck movements occurring in association with speech in young children who stutter.

Significance to Biomedical Research and the Program of the Institute: There is a critical need to stimulate research on stuttering; NINCDS is the prime BID within the U.S. government for the support of stuttering research and only supports one grant in this area. Recent research on adults has indicated some differences in phonatory control between normal and stuttering adults. Research projects need to examine the hypothesis of whether or not children who become persistent stutterers show differences in phonatory control during the normal developmental period of non-fluency.

Objective methods of assessing speech timing control in young children who stutter will provide the necessary tools for research on the development of stuttering in young children. These methods of assessment may lead the way to early identification of young children who are at risk of developing speech dysfluencies and indicate appropriate intervention techniques for improving the development of speech timing control and preventing stuttering.

Cooperating Units: None

Proposed Course: Once the development of the measurement techniques and speech tasks during Phase I is complete and approved by the NINCDS Project Officer, the experimental phase will begin. Phase I will require two years for completion while Phase II will require one year. The contract is expected to terminate in July 1983.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1980 through September 30, 1981

OHIO UNIVERSITY, ATHENS, OHIO (N01-NS-0-2342)

Title: Evaluation of the Effectiveness of Information Services Provided to Specialists in Communicative Disorders by MEDLINE

Contractor's Project Director: William Seaton, Ph.D.

Current Annual Level of Support: $58,550

Objectives: Data will be provided to the NINCDS on MEDLINE users who are specialists in communicative disorders to answer the following questions.

1. What are the information needs of various communicative disorders specialists?
2. Whether various types of specialists in communicative disorders can learn to use terminals for interacting directly with MEDLINE and developing individualized literature searches?
3. Whether MEDLINE provides adequate coverage of research literature in each of the communicative disorders specialties?
4. Which service models (direct access or technical assistance) are most satisfactory for serving the needs of various types of specialists in communicative disorders?
5. Which information needs in various communicative disorders specialties are not met by MEDLINE?

Major Findings: During Phase I, the technical information specialist was trained at the National Library of Medicine and subsequently set up a MEDLINE Center to provide services only to specialists in communicative disorders within the region. All communication disorders specialists in the region were contacted and 42 agreeing to participate in the study completed a pre-use questionnaire gathering information on their professional background, current responsibilities, perceived information needs, current information use and practices, and MEDLINE experience. The pre-use questionnaire data was sent to the NINCDS and is currently being analyzed along with that received from the other four contractors. Two user training workshops were held for all user participants in January and the MEDLINE Center has provided full services to users since that time. Thus far, analysis of monthly reports of user access, type of service model preferred, and level of satisfaction indicates that the majority of users are faculty who prefer to submit searches to be run by the information specialist. Level of satisfaction was high for both submitted and assisted searches.

Significance to Biomedical Research and the Program of the Institute: The Scientific Information Program of the NINCDS has supported activities aimed at providing the rapid transfer of research and technological advances to specialists

in communicative disorders. The Communicative Disorders Program has developed a new approach to meeting the objectives of its Scientific Information Program. MEDLINE services in communicative disorders have been upgraded. A User's Manual and Specialized Thesaurus were published and workshops developed and videotaped to train scientists and clinicians on how to use MEDLINE. These activities are all aimed at enabling users direct access to MEDLINE. In the past, specialized Information Centers have been supported in various specialties to serve users. Such centers are costly and must be maintained through federal funding since users' fees cannot offset the total costs. The new service model developed by the CDP is much less costly since the user learns to access the system directly and is only charged for the online time they require to develop their search and for their hard copy printout.

Cooperating Units: None

Proposed Course: The contract will terminate on 3/14/83.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1980 through September 30, 1981

FATHER FLANAGAN'S BOYS HOME, OMAHA, NEBRASKA (N01-NS-0-2343)

Title: Evaluation of the Effectiveness of Information Services Provided to Specialists in Communicative Disorders by MEDLINE

Contractor's Project Director: Ronald Netsell, Ph.D.

Current Annual Level of Support: $34,379

Objectives: Data will be provided to the NINCDS on MEDLINE users who are specialists in communicative disorders to answer the following questions.

1. What are the information needs of various communicative disorders specialists?

2. Whether various types of specialists in communicative disorders can learn to use terminals for interacting directly with MEDLINE and developing individualized literature searches?

3. Whether MEDLINE provides adequate coverage of research literature in each of the communicative disorders specialties?

4. Which service models (direct access or technical assistance) are most satisfactory for serving the needs of various types of specialists in communicative disorders?

5. Which information needs in various communicative disorders specialties are not met by MEDLINE?

Major Findings: During Phase I, the technical information specialist was trained at the National Library of Medicine and subsequently set up a MEDLINE Center to provide services only to specialists in communicative disorders within the region. All communication disorders specialists in the region were contacted and 181 agreeing to participate in the study completed a pre-use questionnaire gathering information on their professional background, current responsibilities, perceived information needs, current information use and practices, and MEDLINE experience. The pre-use questionnaire data was sent to the NINCDS and is currently being analyzed along with that received from the other four contractors. A user training workshop was held for all user participants in February and the MEDLINE Center has provided full services to users since that time. Thus far, analysis of monthly reports of user access, type of service model preferred, and level of satisfaction indicates that the majority of users are researchers who prefer to submit searches to be run by the information specialist, with a high level of satisfaction.

Significance to Biomedical Research and the Program of the Institute: The Scientific Information Program of the NINCDS has supported activities aimed at providing the rapid transfer of research and technological advances to specialists

in communicative disorders. The Communicative Disorders Program has developed a new approach to meeting the objectives of its Scientific Information Program. MEDLINE services in communicative disorders have been upgraded. A User's Manual and Specialized Thesaurus were published and workshops developed and videotaped to train scientists and clinicians on how to use MEDLINE. These activities are all aimed at enabling users direct access to MEDLINE. In the past, specialized Information Centers have been supported in various specialties to serve users. Such centers are costly and must be maintained through federal funding since users' fees cannot offset the total costs. The new service model developed by the CDP is much less costly since the user learns to access the system directly and is only charged for the online time they require to develop their search and for their hard copy printout.

Cooperating Units: Creighton University Medical School, University of Nebraska Medical School and Medical Center.

Proposed Course: The contract will terminate on 3/14/83.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1980 through September 30, 1981

LOYOLA UNIVERSITY AT CHICAGO, CHICAGO, ILLINOIS (N01-NS-0-2344)

Title: Evaluation of the Effectiveness of Information Services Provided to Specialists in Communicative Disorders by MEDLINE

Contractor's Project Director: William A. Yost, Ph.D.

Current Annual Level of Support: $39,133

Objectives: Data will be provided to the NINCDS on MEDLINE users who are specialists in communicative disorders to answer the following questions.

1. What are the information needs of various communicative disorders specialists?
2. Whether various types of specialists in communicative disorders can learn to use terminals for interacting directly with MEDLINE and developing individualized literature searches?
3. Whether MEDLINE provides adequate coverage of research literature in each of the communicative disorders specialties?
4. Which service models (direct access or technical assistance) are most satisfactory for serving the needs of various types of specialists in communicative disorders?
5. Which information needs in various communicative disorders specialties are not met by MEDLINE?

Major Findings: During Phase I, the technical information specialist was trained at the National Library of Medicine and subsequently set up two MEDLINE Centers to provide services only to specialists in communicative disorders within the region. All communication disorders specialists in the region were contacted and 66 agreeing to participate in the study completed a pre-use questionnaire gathering information on their professional background, current responsibilities, perceived information needs, current information use and practices, and MEDLINE experience. The pre-use questionnaire data was sent to the NINCDS and is currently being analyzed along with that received from the other four contractors. A user training workshop was held for all user participants in February and the MEDLINE Center has provided full services to users since that time. Thus far, analysis of monthly reports of user access, type of service model preferred, and level of satisfaction indicates that the majority of users are graduate students who use the assisted service model with moderate to high satisfaction.

Significance to Biomedical Research and the Program of the Institute: The Scientific Information Program of the NINCDS has supported activities aimed at providing the rapid transfer of research and technological advances to specialists

in communicative disorders. The Communicative Disorders Program has developed a new approach to meeting the objectives of its Scientific Information Program. MEDLINE services in communicative disorders have been upgraded. A User's Manual and Specialized Thesaurus were published and workshops developed and videotaped to train scientists and clinicians on how to use MEDLINE. These activities are all aimed at enabling users direct access to MEDLINE. In the past, specialized Information Centers have been supported in various specialties to serve users. Such centers are costly and must be maintained through federal funding since users' fees cannot offset the total costs. The new service model developed by the CDP is much less costly since the user learns to access the system directly and is only charged for the online time they require to develop their search and for their hard copy printout.

Cooperating Units: Northwestern University, Evanston, Illinois

Proposed Course: The contract will terminate on 3/14/83.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1980 through September 30, 1981

UNIVERSITY OF CONNECTICUT, STORRS, CONNECTICUT (N01-NS-0-2345)

Title: Evaluation of the Effectiveness of Information Services Provided to Specialists in Communicative Disorders by MEDLINE

Contractor's Project Director: Jay Lerman, Ph.D.

Current Annual Level of Support: $53,358

Objectives: Data will be provided to the NINCDS on MEDLINE users who are specialists in communicative disorders to answer the following questions.

1. What are the information needs of various communicative disorders specialists?
2. Whether various types of specialists in communicative disorders can learn to use terminals for interacting directly with MEDLINE and developing individualized literature searches?
3. Whether MEDLINE provides adequate coverage of research literature in each of the communicative disorders specialties?
4. Which service models (direct access or technical assistance) are most satisfactory for serving the needs of various types of specialists in communicative disorders?
5. Which information needs in various communicative disorders specialties are not met by MEDLINE?

Major Findings: During Phase I, the technical information specialist was trained at the National Library of Medicine and subsequently set up a MEDLINE Center to provide services only to specialists in communicative disorders within the region. All communication disorders specialists in the region were contacted and 104 agreeing to participate in the study completed a pre-use questionnaire gathering information on their professional background, current responsibilities, perceived information needs, current information use and practices, and MEDLINE experience. The pre-use questionnaire data was sent to the NINCDS and is currently being analyzed along with that received from the other four contractors. Two user training workshops were held for all user participants in February and the MEDLINE Center has provided full services to users since that time. Thus far, analysis of monthly reports of user access, type of service model preferred, and level of satisfaction indicates that most users are clinicians or students who prefer the assisted model of use, with high to moderate satisfaction.

Significance to Biomedical Research and the Program of the Institute: The Scientific Information Program of the NINCDS has supported activities aimed at providing the rapid transfer of research and technological advances to specialists

in communicative disorders. The Communicative Disorders Program has developed a new approach to meeting the objectives of its Scientific Information Program. MEDLINE services in communicative disorders have been upgraded. A User's Manual and Specialized Thesaurus were published and workshops developed and videotaped to train scientists and clinicians on how to use MEDLINE. These activities are all aimed at enabling users direct access to MEDLINE. In the past, specialized Information Centers have been supported in various specialties to serve users. Such centers are costly and must be maintained through federal funding since users' fees cannot offset the total costs. The new service model developed by the CDP is much less costly since the user learns to access the system directly and is only charged for the online time they require to develop their search and for their hard copy printout.

Cooperating Units: None

Proposed Course: The contract will terminate on 3/14/83.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1980 through September 30, 1981

UNIVERSITY OF HAWAII AT MANOA, HONOLULU, HAWAII (N01-NS-0-2346)

Title: Evaluation of the Effectiveness of Information Services Provided to Specialists in Communicative Disorders by MEDLINE

Contractor's Project Director: James Yates, Ph.D.

Current Annual Level of Support: $50,884

Objectives: Data will be provided to the NINCDS on MEDLINE users who are specialists in communicative disorders to answer the following questions.

1. What are the information needs of various communicative disorders specialists?
2. Whether various types of specialists in communicative disorders can learn to use terminals for interacting directly with MEDLINE and developing individualized literature searches?
3. Whether MEDLINE provides adequate coverage of research literature in each of the communicative disorders specialties?
4. Which service models (direct access or technical assistance) are most satisfactory for serving the needs of various types of specialists in communicative disorders?
5. Which information needs in various communicative disorders specialties are not met by MEDLINE?

Major Findings: During Phase I, the technical information specialist was trained at the National Library of Medicine and subsequently set up two MEDLINE Centers to provide services only to specialists in communicative disorders within the region. All communication disorders specialists in the region were contacted and 120 agreeing to participate in the study completed a pre-use questionnaire gathering information on their professional background, current responsibilities, perceived information needs, current information use and practices, and MEDLINE experience. The pre-use questionnaire data was sent to the NINCDS and is currently being analyzed along with that received from the other four contractors. Two user training workshops were held for all user participants in March and the MEDLINE Center has provided full services to users since that time. Thus far, analysis of monthly reports of user access, type of service model preferred, and level of satisfaction indicates that the majority of users are clinicians who use the assisted service model with moderate to high satisfaction.

Significance to Biomedical Research and the Program of the Institute: The Scientific Information Program of the NINCDS has supported activities aimed at providing the rapid transfer of research and technological advances to specialists

in communicative disorders. The Communicative Disorders Program has developed a new approach to meeting the objectives of its Scientific Information Program. MEDLINE services in communicative disorders have been upgraded. A User's Manual and Specialized Thesaurus were published and workshops developed and videotaped to train scientists and clinicians on how to use MEDLINE. These activities are all aimed at enabling users direct access to MEDLINE. In the past, specialized Information Centers have been supported in various specialties to serve users. Such centers are costly and must be maintained through federal funding since users' fees cannot offset the total costs. The new service model developed by the CDP is much less costly since the user learns to access the system directly and is only charged for the online time they require to develop their search and for their hard copy printout.

Cooperating Units: Hawaii Medical Library, Honolulu

Proposed Course: The contract will terminate on 3/14/83.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1981 through September 30, 1981

MEDICAL UNIVERSITY OF SOUTH CAROLINA (N01-NS-1-2381)

Title: An Analytical Study of the Auditory Effects of Noise

Contractor's Project Director: John H. Mills, Ph.D.

Current Annual Level of Support: $120,000

Objectives: To prepare an analysis of current knowledge of the auditory effects of noise and propose possible research methods, data collection and analytical procedures that will address specific questions to be developed as program initiatives by the Communicative Disorders Program.

Major Findings: Present work involves the preparation of an outline of the following topics for inclusion in the analytical review: differential diagnosis and measurement of noise-induced hearing loss; individual differences and susceptibility; protection and conservation of hearing; anatomy; physiology; biochemistry; temporary threshold shift (TTS); permanent threshold shift (PTS); asymtotic threshold shift (ATS); relation of existing sensorineural hearing loss and TTS, PTS, and ATS; noise and other ototraumatic agents; and continuous, intermittent and impulse noise.

Significance to Biomedical Research and the Program of the Institute: This project addresses Goal #68 identified in the National Research Strategy for NINCDS which states: Determine the causes of acquired sensorineural hearing losses, especially the effects of aging, drug toxicity and environmental pollutants such as noise, in order to move toward prevention.

Cooperating Units: None

Proposed Course: Contract was initiated on July 1, 1981; completion of four phases of work is expected by July 1983.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1981 through September 30, 1981

TO BE AWARDED IN FY 1981 (RFP-NIH-NINCDS-81-05)

Title: High Frequency Hearing Assessment

Contractor's Project Director: To be determined.

Current Annual Level of Support: $150,000

Objectives: To develop and evaluate an electroacoustic device to be used for valid and reliable assessment of human hearing thresholds in the frequency range of 8 to 20 kHz with particular emphasis on the transducer unit and signal processing capabilities of the audio-generator.

Major Findings: Contract to be awarded in last quarter of FY 1981.

Significance to Biomedical Research and the Program of the Institute: This project was developed in response to Goal #65 identified in the National Research Strategy for NINCDS which states: Research on the identification and quantification of auditory function, in order that patients with hearing disorders and diseases may be properly evaluated and effectively treated.

Cooperating Units: None

Proposed Course: Three years of work are expected to design the transducer and methodology for coupling the transducer to the eardrum; develop the audiometer circuitry and calibration procedures; and, evaluate the device on a population of otologically normal young adults.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02185-07 CDP

PERIOD COVERED
October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

Characteristics of Dysarthric Speech Associated with Neurologic Disease

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.	C.L. Ludlow, Speech Pathologist, CDP, NINCDS
Other:	C.J. Bassich, Speech Pathologist, CDP, NINCDS
	R. Eldridge, Neurologist, IRP, NINCDS
	R. Polinsky, Neurologist, LCS, NIMH

COOPERATING UNITS (if any)

IRP, NINCDS
LCS, NIMH

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.35	.25	.10

CHECK APPROPRIATE BOX(ES)
☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The long range goal is to determine the distinctive patterns of speech motor control disturbances (dysarthrias) associated with neuromotor diseases/disorders resulting from pathology in different regions of the central nervous system. Acoustic measures have been developed which identify the oral structure involved in the speech disturbance and the type of disturbance which have validity for differentiating between normal and pathological speakers of the same age and sex as well as between patients with different types of neuromotor disease/disorder. Studies are ongoing aimed at determining how speech planning is disturbed in various types of neurological disorders for the purpose of gaining insight into the degree of movement integration present at various levels in the speech motor control system. The place of occurrence of involuntary movements in speech syllables, words, phrases and sentences will be determined as well as the degree of disruption in the speech rhythm in segments of various lengths in syndromes such as Huntington's Chorea, Tardive Dyskinesia, Gilles de la Tourette Syndrome and Dystonia.

PROJECT DESCRIPTION

Objectives:

1. To determine which measures of speech motor control are useful for identification of particular types of speech disturbances resulting from neurological diseases/disorders at different levels of the CNS.

2. To determine which measures of speech motor control are indicative of early stages of Huntington's chorea and are valid indicators of degree of disease progression.

3. To determine at what points in speech organization, involuntary movements intrude in the speech process in various neurological diseases/disorders to indicate the degree of speech planning occurring at each level in the nervous system.

4. To determine how the speech rhythm is altered by the occurrence of movement perturbations at different points in speech segments as an indication of the size of units involved in speech planning.

Methods Employed: All patients are tested in a sound controlled environment with intensity and frequency calibration using an acoustic microphone, accelerometer, contact microphone and laryngograph. Acoustic analysis of phonatory frequency, intensity and perturbation, articulatory timing and formant structure are conducted with a sound spectrograph, graphic level recorder, and a pitch tracking microprocessor. Measures are made with a small laboratory computer and an x-y digitizer and microprocessor. The acoustic analyses and measurements are made without knowledge of speaker identity and drug-placebo state. The reliability of all measures is greater than .90. Measures are assessed statistically for degree of independence and variables selected which are independent measures of speech motor control attributes and discriminate between patients and controls and between different types of dysarthria. Twenty-eight measures have been identified as independent measures of the following attributes: speech rate control; control of complex articulation; voicing control; fundamental frequency control; control of speech segment timing; and control of speech intensity.

More recently, lip and jaw movements are measured with a universal movement transducer. This instrument was developed by Mr. Eli Walker of Biomedical Engineering, NIH for this purpose. It is non-invasive and does not disturb the speech production process. Displacement, velocity and acceleration of lip and jaw movement in three separate dimensions, anterior/posterior, inferior/superior and lateral/medial is processed for selected speech segments to determine the rate of articulator movement during speech.

Subjects Tested: Ten patients have been tested in each of the following groups: Hypokinetic Parkinson's disease; tardive dyskinesia with bucco-linguo-masticatory (BLM) syndrome; Huntington's chorea with high risk family members; and, multiple systems atrophy (Shy-Drager syndrome). Thirty normal aging controls of each sex have also been tested.

Major Findings:

1. The speech symptoms found to differentiate between patients with hypokinetic Parkinson's disease and those with multiple systems atrophy (Shy-Drager) were as follows: slow speech rate, equalized stress on all speech syllables, intermittent diplophonia (glottal fry), strain strangle voice quality, and low speech intensity.

2. The profile of speech disturbance in hypokinesia in Parkinson's disease is severely reduced laryngeal abduction during vowel repetition, reduced range in speech intensity, limited duration of phonation, reduced rate control during speech articulation, and increased latency of tongue movement for speech articulation.

3. The profile of speech disturbance in BLM tardive dyskinesia is reduced range in fundamental frequency, reduced rate of laryngeal abduction and adduction during vowel repetition, reduced rate of speech articulation, and reduced range in speech intensity.

4. Although vocal hoarseness is a perceptual symptom of speech production in several dysarthric syndromes, fundamental frequency perturbation did not differ from normal in either patients with Parkinson's disease or Shy-Drager syndrome.

5. The perceptual symptom of glottal fry was associated with the occurrence of diplophonia of fundamental frequency in Shy-Drager syndrome, demonstrating that this mode of vocal fold vibration may result from alteration in laryngeal abductor paresis.

Significance to Biomedical Research and the Program of the Institute: The development of objective procedures for the assessment and differential diagnosis of various types of dysarthria in adults with neurological diseases, will enable researchers and clinicians to evaluate different treatments for these patients. The information being gained on which speech production processes are particularly impaired in each of the neurological diseases, will contribute to our understanding of the organization of speech motor control within the central nervous system.

Proposed Course: Three manuscripts have been submitted for publication based on studies completed. A new series of studies of the disturbance of speech timing with involuntary movements have been initiated.

Publications:

Ludlow CL. Directions for the development of improved methods for assessing vocal pathology. ASHA Reports, in press.

Ludlow CL, Coulter D, Gentges F. The differential sensitivity of measures of fundamental frequency perturbation to laryngeal neoplasms and neuropathologies. In Bless D, Abbs J, eds. Vocal Fold Physiology, University of Wisconsin Press, in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02247-05 CDP

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

The Characteristics and Treatment of Vocal Tics and Language Processing in Gilles de la Tourette Syndrome

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.	C.L. Ludlow, Speech Pathologist, CDP, NINCDS
Other:	C.J. Bassich, Speech Pathologist, CDP, NINCDS
	R. Polinsky, Neurologist, LCS, NIMH

COOPERATING UNITS (if any)

IR, NIMH

LAB/BRANCH

Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .35	PROFESSIONAL: .25	OTHER: .10

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A series of research studies are being conducted to determine the following:

1. The characteristics of vocal tic phenomena in Gilles de la Tourette Syndrome.

2. The differential effects of various neuropharmacological treatments on the type and severity of vocal tics in patients with Gilles de la Tourette Syndrome.

3. The relationship of vocal tic production to propositional language behavior and speech fluency.

4. Whether history of tics, Tourette Syndrome or stuttering in patients' family history are predictive of the vocal tic and language dysfunctions seen in patients with Tourette syndrome.

PHS-6040
(Rev. 2-81)

PROJECT DESCRIPTION

Objectives: To determine: the characteristics of Gilles de la Tourette (GT) syndrome; the relationships between various vocal tic symptomatology in GT; the relationship of language processing deficits to vocal and motor tic symptomatology in GT; the differential characteristics of speech dysfluency in GT from stuttering; the predictive relationship of familial history with the severity and type of vocal tic and language processing deficits in GT syndrome; and, the efficacy of various neuropharmacological agents in the treatment of GT.

Procedures: Calibrated speech recordings are made in a sound controlled environment. Oscillographic tracings are used to measure pause durations in connected speech and the place of occurrence of vocal tics relative to speech onset. Language processing skills are assessed using a standardized battery as well as an experimental battery assessing rate of nominative retrieval, recall of nominative material presented by speech, in writing and pictorally, and comprehension of complex directions presented by speech, in writing or by gesture. Laterality of speech perception during dichotic listening is assessed using minimal pair contrasts of CV syllables. Reading skills are assessed using the Gates-McKillop Diagnostic Battery. All tests are scored without knowledge of the subjects identity (GT or age and sex matched control) or placebo-drug state (Placebo, Haloperidol or Lecithin).

Subjects: Subjects are seen on an outpatient basis following diagnosis of GT syndrome according to Shapiro's five criteria. Initial speech and language assessment are done after patients have been off all medications for at least two weeks. Only those admitted as inpatients are retested twice weekly during drug-placebo double blind cross-over studies.

Major Findings:

1. GT patients have reduced spontaneous speech output in comparison with normals of the same age and sex although their speech rate does not differ from normal.

2. Although total vocal tic production is significantly greater than normal in GT patients only certain vocal tic types are significantly greater in GT patients. These are laryngeal, nasal, respiratory, and labial tics. The only vocal tic type not produced by normals was coprolalia; this tic type was produced by 35% of GT patients.

3. GT patients of all ages, children (5 to 11 years), adolescents (12 to 18 years) and adults were significantly impaired in comparison with normal on oral language expression subtests but were unimpaired on tests of speech repetition, oral reading, reading comprehension and language comprehension. The only other language deficits were in written expression.

4. These language expression deficits in association with reduced speech output are similar in nature to transcortical motor aphasia, demonstrate an involvement in higher cortical functioning in GT unrelated to vocal tic production and may reflect dysfunction in the supplementary motor and speech areas.

Significance to Biomedical Research and the Program of the Institute: This research has both basic and applied significance for the understanding and treatment of this syndrome. First, the demonstration of a language performance deficit not associated with vocal tic symptomatology indicates that the pathology involves more than basal ganglia mechanisms and that cortical functioning is also altered in this syndrome. Second, the demonstration of a continuum of vocal tic symptomatology provides a scale by which the severity of syndrome involvement can be assessed in patients with different symptoms. Finally, the study of individuals' responses to acute neuropharmacological manipulations provides information on the possible biochemical bases for this syndrome.

Proposed Course: Over 50 patients with GT syndrome ranging in age from 5 to 65 years and age and sex matched normal controls have completed speech and language testing. Data analysis is ongoing examining the relationship between family history of speech and language disorders and stuttering and the occurrence and severity of speech and language involvement in GT syndrome.

Publications:

Ludlow CL, Polinsky RJ, Caine ED, Bassich CJ, Ebert MH. Language and speech abnormalities in Tourette syndrome. In Chase T, Friedhoff A, eds. Tourette Syndrome, Raven Press, New York, in press.

Caine ED, Polinsky RJ, Ludlow CL, Ebert MH, Nee LE. Heterogeneity and variability in Tourette Syndrome. In Chase T, Friedhoff A, eds. Tourette Syndrome, Raven Press, New York, in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02336-04 CDP

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Cis Platinum and Early Identification of Ototoxicity

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. E. Elkins, Audiologist, CDP, NINCDS
Other: A. Pikus, Audiologist, CC
A. Grimes, Audiologist, CC

COOPERATING UNITS (if any)

Radiation Oncology Branch, NCI
Division of Cancer Treatment, NCI
Clinical Center, NIH

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .02	PROFESSIONAL: .02	OTHER: .00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Cisplatinum used in the treatment of testicular and ovarian cancer is known to have toxic effects upon the hearing of patients. Cochlear damage is manifest by a high-frequency hearing loss and general difficulty in understanding normal speech conversation. Periodic assessment of pure tone thresholds and suprathreshold speech perception are being conducted to evaluate and relate degree and progression of ototoxicity to drug dosage and frequency of administration.

PHS-6040
(Rev. 2-81)

PROJECT DESCRIPTION

Objectives: To develop techniques for the assessment of ototoxicity related to the administration of certain chemotherapeutic agents employed in cancer treatment. The following areas are being addressed: a) type of hearing loss, b) onset and degree of loss relative to dosage and preexisting hearing condition, c) documentation of onset of tinnitus and/or vertigo, d) predisposition to ototoxic effects, e) unilateral/bilateral symmetrical loss, f) suprathreshold speech perception, g) prediction of probable ototoxicity, and h) possible reversibility of ototoxic effects.

Methods Employed: In addition to routine procedures and speech in ipsilateral noise, monosyllabic words and sentence stimuli are presented at various signal-to-noise ratios (S/N) and at different levels above puretone or speech reception threshold levels.

Major Findings: Phase II data collection is continuing with a selected group of subjects. Lack of constant referral by the attending physicians has slowed progress this year. In addition, documentation of drug dosages has not always been complete so a number of patients evaluated have not been entered into the data analyses due to incomplete information. It is essential that all variations of the experimental drugs be identified along with the dosage and frequency of administration.

Significance to Biomedical Research and the Program of the Institute: The development of repeatable and valid methods of assessing hearing impairment following the administration of known drug dosages would provide the clinician with documentation for the managing physicians who in turn may reassess their drug protocols. A reliable method of predicting ototoxicity is definitely needed if prevention of impairment is to be realized.

Proposed Course: Further investigation will be given to the problems and procedures identified above with a patient population available through cooperation with the National Cancer Institute.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02337-04 CDP

PERIOD COVERED

October 1, 1980 to September 30, 1981

TITLE OF PROJECT (80 characters or less)

The Effects of Stimulants on the Auditory Processing and Language Skills of Hyperactive, Language Impaired and Normal Subjects

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. C.L. Ludlow, Speech Pathologist, CDP, NINCDS
Other: J.L. Rapoport, Psychiatrist, IR, NIMH
G.L. Brown, Psychiatrist, IR, NIMH
C.J. Bassich, Speech Pathologist, CDP, NINCDS

COOPERATING UNITS (if any)

IR, NIMH

LAB/BRANCH

Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .50	PROFESSIONAL: .25	OTHER: .25

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A series of studies are being conducted to determine the following:

1. What the effects of stimulants are on the speech and language production of language-disordered hyperactive boys;

2. Whether auditory processing disorders in hyperactive boys with and without disorders in speech, language and reading respond similarly to the administration of dextroamphetamine;

3. Whether the effects of stimulant drugs on auditory processing disorders in language-impaired children are related to the effects of stimulants on language processing and speech fluency;

4. Whether auditory processing disorders are related to speech perception discrimination curves in hyperactive boys with and without language disorders.

PHS-6040
(Rev. 2-81)

PROJECT DESCRIPTION

Objectives: To determine:

1. Whether dextroamphetamine has a beneficial effect on the auditory processing skills of language disordered boys;

2. Whether an MAO inhibitor has similar effects to dextroamphetamine on the language processing, speech fluency, and auditory processing behaviors of hyperactive boys;

3. Whether hyperactive boys who have normal speech, language and reading skills, have auditory processing deficits similar to those found in language impaired boys;

4. Whether dextroamphetamine similarly affects auditory processing skills in language impaired hyperactive boys and hyperactive boys who are without speech, language or reading disorders.

Procedures: On admission to the study each subject receives a complete battery of standardized tests of speech, language, reading, intelligence and behavior by a multidisciplinary team.

Modular programming equipment is used to program the administration of acoustic stimuli, record subjects responses and their reaction times during four auditory processing experiments assessing threshold in noise, vigilance, mean reaction time, gap detection and temporal order processing (after Hirsh and Sherrick).

Speech discrimination testing is conducted and speech perception for synthesized speech stimuli test the gap size critical for discrimination of /sa/ from /sta/ and the inter-stimulus interval critical for correct identification of phoneme order for discrimination of /sa/ from /as/.

Speech production is recorded during a communication barrier game in which subjects must direct a listener on how to construct block designs without visual feedback. All speech production is transcribed and the rate of speech production (words/min.), and the number of dysfluencies between and within words are tabulated.

All subject testing and data analysis is performed without knowledge of drug-placebo condition. Experiments involving dextroamphetamine and an MAO inhibitor involve different subjects and both are double-blind counterbalanced crossover trials of drug and placebo conditions.

Major Findings:

1. Similar deficits in processing the temporal order of rapidly occurring acoustic stimuli were found in hyperactive boys without language and learning disorders, hyperactive boys with learning disorders and language impaired boys. Thus the correlation between the presence of language disorder and auditory processing deficits was not substantiated, bringing into question the view that auditory processing disorders are the basis for disordered language development in young children.

2. Training on auditory processing tasks was found to improve the perception of temporal order of acoustic stimuli in hyperactive boys with and without learning disorders although their attention disorders were not improved with training.

3. The effects of dextroamphetamine on attention and auditory processing in hyperactive boys with and without language and learning disorders were dissimilar. The stimulant drug improved the attention disorder to within the normal range in both groups of hyperactive boys.

4. However, the deficits in auditory processing were improved with dextroamphetamine only in the hyperactive boys who were without language or learning disorders. Although the hyperactive boys with language and learning disorders were significantly improved in attention, their auditory processing disorders were not improved with dextroamphetamine. These findings indicate that the auditory processing disorders in these two groups have different neurological bases. In the hyperactive boys without a language or learning disorder, the auditory processing disorders may result from attentional deficits and both disorders improved with drug. In the language and learning disabled boys only the attentional disorder was improved with a stimulant and not the processing disorder. The latter may be an additional perceptional deficit which is best improved through training rather than drug treatment.

Significance to Biomedical Research and the Program of the Institute: Recently a great deal of attention has focused on the auditory processing deficits of language impaired children and adults. Training programs aimed at improving these skills in language impaired children are now prolific and are based on the assumption that such deficits are either the basis of or contribute to the language disorder in such children. The finding that such auditory processing disorders exist in children who are without deficits in reading, language or speech brings this assumption into question. Rather, such deficits may be a more general sign of many different types of cognitive disorders.

Proposed Course: Papers on completed studies have been submitted for publication. Data collection is now proceeding on the effects of an MAO inhibitor on auditory processing, attention, and language processing. Experiments investigating the relationship between speech perception and auditory processing deficits in hyperactive and language impaired boys have been initiated.

Publications:

Rapoport JL, Buchsbaum MS, Weingartner H, Zahn T, Ludlow C, Mikkelsen E. Dextroamphetamine: Cognitive and behavioral effects in normal and hyperactive children and normal adults. Archives of General Psychiatry, 1980; 37: 933-43.

Ludlow CL. Impaired language development: Hypotheses for research. Bulletin of the Orton Society, 1980; 30: 153-69.

Caine E, Weingartner H, Ludlow C, Cudahy E, Wehry S. Qualitative analysis of scopolamine induced amnesia. Psychopharmacologica, in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do **NOT** use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 NS 02395-03 CDP

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Analysis of Fluctuating Hearing Loss Associated with Cogan's Syndrome

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. A. Pikus, Audiologist, CC
Other: B. F. Haynes, LCI, NIAID
E. Elkins, Audiologist, CDP, NINCDS

COOPERATING UNITS (if any)

Clinical Center, NIH
Laboratory of Clinical Investigation, NIAID

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .05	PROFESSIONAL: .05	OTHER: .00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

To assess the course of the auditory deficit associated with Cogan's Syndrome. Six patients have been audiologically evaluated following treatment with corticosteroids and/or diuretic therapy.

PROJECT DESCRIPTION

Objectives: To develop accurate audiologic indices of the pattern of hearing deficit in Cogan's Syndrome and to document relationship of hearing deficit to therapy.

Methods Employed: Standard audiologic test battery is utilized weekly or biweekly including middle ear analysis. Special auditory tests are repeated intermittently to verify the cochlear nature of the auditory effects of this disease process.

Major Findings: All six patients have presented with interstitial keratitis, vertigo, tinnitus and sensorineural hearing loss. Following corticosteroid treatment, all subjects showed an initial improvement in hearing for pure tones and speech. Subsequent fluctuations in hearing were unresponsive to corticosteroids. Appropriate case management for these patients is under development. Previous findings appear to be maintained to date.

Significance to Biomedical Research and the Program of the Institute: The development of an audiological profile of subjects with Cogan's Syndrome should provide clinicians with information for successful management of these patients.

Proposed Course: Periodic reassessment of Cogan's Syndrome patients is required to follow long-term course of auditory anomalies.

Publications: Haynes BF, Pikus A, Kaiser-Kupfer M, Fauci AS. Successful treatment of sudden hearing loss in Cogan's Syndrome with corticosteroids. Journal of Arthritis and Rheumatism 1981; 24: 501-3.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02396-03 CDP

PERIOD COVERED

October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Auditory Deficits in Osteogenesis Imperfecta**

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. A. Pikus, Audiologist, CC, NIH
Other: E. Elkins, Audiologist, CDP, NINCDS
E. Gross, Chief, Molecular Structure Section, ERRB, NICHD
J. W. Hansen, Pediatrician, Developmental Biology & Clinical Nutrition Section, NPMB, NICHD
S. Levin, Dept. of Otolaryngology, Johns Hopkins University
K. Rosenbaum, Dept. of Genetics, Children's Hospital, Washington, D.C.
D. Rowe, Dept. of Pediatrics, University of Connecticut

COOPERATING UNITS (if any)

LDBA, NIDR; CC, NIH; Molecular Structure Section, ERRB, NICHD; Developmental Biology & Clinical Nutrition Section, NPMB, NICHD; Johns Hopkins University; University of Connecticut; Children's Hospital, Washington, D.C.

LAB/BRANCH

Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.10	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Methods are being developed to delineate the types of hearing losses associated with Osteogenesis Imperfecta (OI). Measurement of middle ear function by tympanometry and acoustic reflexes are being developed to classify penetrance and types of auditory deficits associated with differing forms of this disease.

**[This study is the NINCDS portion of a larger study (CC) entitled: "Collagen Metabolism in Osteogenesis Imperfecta (OI)," of which Dr. Jay R. Shapiro is the Principal Investigator.]

PHS-6040
(Rev. 2-81)

PROJECT DESCRIPTION

Objectives: This study evaluates all OI patients for audiologic abnormalities, using the standard threshold and suprathreshold techniques with special emphasis on middle ear analysis, in an effort to classify the different kinds and severity of hearing loss and perhaps identify carrier status in certain types as well as middle ear factors related to prognosis for future audiologic deficit. Complete families of patients are now being evaluated as well.

Methods Employed: Routine audiologic battery: consisting of pure tone and speech threshold measurements; suprathreshold discrimination for speech; tolerance levels for speech under headphones; tympanometry and the measurement of contralateral acoustic reflexes. Special auditory tests are administered as indicated.

Major Findings: The peripheral auditory deficits associated with OI have been studied in over 100 patients and family members with a special emphasis on middle ear function analysis. A significant number of patients and supposedly unaffected family members have demonstrated abnormalities in tympanometry and acoustic reflex measurements. A specific pure tone sensorineural deficit has emerged in the patients with OI. This configuration, known as CHOI (characteristic of OI), is found in a significant number of patients and "supposedly unaffected" family members.

Significance to Biomedical Research and the Program of the Institute: Identification of carrier status in OI by means of an easily administered audiologic evaluation would have great value in the management of families in which OI is prominent.

Proposed Course: This project is ongoing and will continue to assess the parameters mentioned above.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 NS 02440-02 CDP

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)
The Development of Acoustic Measurement Tools for Assessing Vocal Pathology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.	C.L. Ludlow, Speech Pathologist, CDP, NINCDS
Other:	R. Naunton, Director, CDP, NINCDS
	C. Bassich, Speech Pathologist, CDP, NINCDS
	R. Eldridge, Neurologist, IRP, NINCDS

COOPERATING UNITS (if any)
IRP, NINCDS and National Naval Medical Center

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.50	.25	.25

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose is to determine the sensitivity of various acoustic measures to vocal pathology associated with laryngeal diseases/disorders including laryngeal carcinoma, vocal polyps, vocal nodules and contact ulcers. Acoustic assessment procedures will provide an objective means of quantifying voice disorders or dysfunctions, and evaluating the effects of various treatments on vocal pathologies.

A microprocessor has been developed for quantifying frequency perturbation (jitter) while a similar system has been developed for quantifying amplitude perturbation (shimmer). Both measurement techniques have improved resolution over previous methods of measurement, and provide indices of vocal function which are stable across normal adults with different fundamental frequencies.

PROJECT DESCRIPTION

Objectives: To determine whether measures of frequency perturbation and amplitude perturbation and various processing algorithms can be developed which will:

1. Accurately identify patients with early signs of laryngeal disease and discriminate them from normal adults of the same age and sex;
2. Assess the degree of vocal dysfunction in various forms of laryngeal pathology;
3. Relate to the size and location of laryngeal pathology;
4. Relate to perceptual judgements of degree of vocal dysfunction;
5. Accurately reflect changes in vocal function following successful treatment of vocal nodules and polyps;
6. Differentiate between different types of phonatory disorders with different etiologies.

Procedures: Both patients and normal volunteers receive the following examinations: direct fiberoptic nasopharyngolaryngoscopy, an extensive medical history on laryngeal and respiratory health, smoking, drinking and vocal abuse; and speech recording with an acoustic microphone, an accelerometer and laryngograph. Recordings are analyzed through microprocessors which filter and select glottal periods and peaks for measuring individual cycle lengths and amplitudes. The resulting signals are digitized and further processed using measurement algorithms on a dedicated laboratory computer.

Three speech pathologists have been trained over a three month period to judge extended phonations on twelve different attributes of pitch, loudness and quality. Intra-class correlation coefficients for all judgements are greater than .90.

Subjects: Diagnosed cases of vocal pathology due to neoplastic growths on the larynx including carcinoma, polyps, nodules or contact ulcers, and normal volunteers of the same age and sex characteristics are being studied at the NIH as outpatients. Normal volunteers comprise two groups: one group includes a random selection of normal volunteers with histories of smoking and/or drinking; the second group are active members of the Mormon Church who neither smoke nor drink.

Major Findings:

1. A study of the lower limits of frequency perturbation in non-smoking and non-drinking normal adults indicated a lower limit of 13.00 μsec. in normal young speakers well above the measurement resolution of the system (3.9 μsec.). This value is 20 μsec. lower than previously reported.
2. Three patterns of frequency perturbation were identified in normal speech: type A with regular cycle by cycle perturbation; type B with random variation in cycle by cycle perturbation; and, type C with intermittent or continuous diplophonia.
3. The Jitter Ratio measurement parameter differentiated between the three different patterns of frequency perturbation.

4. A significant ($p \leq .02$) linear relationship between age and fundamental frequency perturbation was found in both male and female normal adults. This relationship continued to be significant when applied across adults differing in their alcohol and tobacco habits. These changes in phonatory functioning may be related to the reduction in muscle fibers in the cricoarytenoid muscle associated with aging.

5. Measures of frequency perturbation were compared in three groups of patients all with phonatory disorders of different etiologies to determine whether these measures could differentiate these groups. One group had laryngeal polyps, a second had Parkinson's disease while the third had significant abductor paresis (Shy-Drager syndrome).

   The only group with significantly greater mean perturbations than age and sex matched controls was the group with laryngeal neoplasms. The Parkinson patients were within normal range on all of the measurement patterns and the Shy-Drager patients only exhibited increased scores on the Diplophonia Ratio demonstrating a different mode of phonation occurring in these patients.

   Thus, although all three groups had perceptually similar voice disorders, the acoustic measures accurately differentiated between them.

Significance to Biomedical Research and the Program of the Institute: Objective procedures are being developed for measuring vocal function in patients with laryngeal pathology. Such procedures are needed for non-invasive assessment of individuals at high risk for laryngeal pathology. Those individuals found to have early signs of vocal pathology would then be referred to an otolaryngologist for a laryngeal examination and monitored on a regular basis for changes in laryngeal functioning. Such objective measurement procedures are needed for evaluating the adequacy of patients' laryngeal function for phonation. At present, only perceptual judgements of the otolaryngologist and/or speech pathologist are available for evaluating the effects of treatment or degree of pathology in phonatory functioning.

Proposed Course: Manuscripts on the studies completed have been submitted for publication. Data collection is ongoing on studies aimed at determining the sensitivity of acoustic measures to changes in laryngeal structure and range of movement; the relationship between acoustic measures of phonatory function and the size and location of laryngeal neoplasms; and, the relationship between acoustic measures of phonatory function and neuromuscular disorders of laryngeal functioning.

Publications:

Ludlow CL, Hart MO. The assessment of vocal pathology. ASHA Reports, in press.

Ludlow CL, Coulter D, Gentges F. The differential sensitivity of measures of fundamental frequency perturbation to laryngeal neoplasms and neuropathologies. In Bless D, Abbs J, eds. Vocal Fold Physiology. University of Wisconsin Press, in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02441-02 CDP

PERIOD COVERED
October 1, 1980 through September 31, 1981

TITLE OF PROJECT (80 characters or less)

Hearing Assessment in Central Neurofibromatosis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. E. Elkins, Audiologist, CDP, NINCDS
Other: A. Pikus, Audiologist, CC
R. Eldridge, Chief Clinical Neurogenetics

COOPERATING UNITS (if any)
Clinical Center Audiology
Clinical Neurogenetics Branch, NINCDS
Cancer Epidemiology Branch, NCI

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.10	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This autosomal dominantly inherited form of neurofibromatosis (NF) usually occurs without the visible stigmata of peripheral NF and is characterized by bilateral acoustic tumors. Complete families are being studied, including children, in order to provide earlier and more accurate diagnoses of tumors. Appropriate and timely medical and audiological management plus counseling are considered for each patient individually.

PHS-6040
(Rev. 2-81)

PROJECT DESCRIPTION

Objectives: To develop reliable techniques for the assessment of hearing disorders associated with central neurofibromatosis. We are cooperating with specialists in genetics and genetic counseling, neurology, neurosurgery, orthopedics, physical medicine and rehabilitation, otolaryngology, dermatology, radiology and cancer to develop recommendations for treatment of these patients and their families. Bilateral acoustic neuromas, which are a hallmark of this form of neurofibromatosis, are being documented in this study.

Methods Employed: In addition to routine procedures, evoked potentials to acoustic stimuli presented through earphones are being obtained. With an active electrode placed on vertex of the hand, a reference electrode on the earlobe receiving the stimuli, and a ground electrode on the contralateral earlobe, we record responses which occur within 10 msec after click stimulation. The intensity of the signals ranges from inaudible levels up to 125 dB sound pressure level (SPL). Levels of stimuli presentation are selected for the individual subject. At no time is the subject sedated.

Major Findings: No definitive findings are reportable at this time. Tentatively, we feel that abnormal amplitudes and latencies of Waves 1-3 are indicative of probable eighth nerve involvement.

Significance to Biomedical Research and the Program of the Institute: This project relates to the National Research Strategy Goal #65 which states: Research on the identification and qualification of auditory function, in order that patients with hearing disorders and diseases may be properly evaluated and effectively treated.

Proposed Course: Normative evoked potential data has been developed and provides the bases to which data from patients may be compared. The parameter of pulses per second stimulus presentation will be altered as findings dictate.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02470-01 CDP

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Audiologic Findings in an Aging Population*

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. A. Pikus, Audiologist, CC
Other: A. Grimes, Audiologist, CC
E. Elkins, Audiologist, CDP, NINCDS
C. Robertson-Chabo, LN, GRC, NIA
B. Margolin, LN, GRC, NIA
R. Duara, LN, GRC, NIA

COOPERATING UNITS (if any)
Clinical Center
Laboratory of Neurosciences, Gerontology Research Center,
National Institute on Aging

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.20	.20	.00

CHECK APPROPRIATE BOX(ES)
☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The assessment of auditory function on "normal" subjects is being obtained through an Institute on Aging protocol investigating regional brain metabolism. Subjects are given detailed audiologic assessment test batteries to provide information towards developing a profile on risk factors for presbycusis.

*Part of larger study with Institute on Aging

PROJECT DESCRIPTION

Objectives: To develop a profile on risk factors for presbycusis.

Methods Employed: In addition to a basic audiologic evaluation, several special procedures including, high frequency pure tone testing, Performance Intensity functions, bilateral fusion, filtered speech tests and ABR procedures are employed.

Major Findings: Preliminary findings indicate depressed threshold measures in the high frequency range for subjects age 50 years and older.

Significance to Biomedical Research and the Program of the Institute: The NINCDS National Research Strategies Report stated in Goal #68: Determination of the causes of acquired sensorineural hearing losses, especially the effects of aging, drug ototoxicity, and environmental pollutants such as noise, in order to move toward prevention.

Proposed Course: Two years are expected for this project.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02471-01 CDP

PERIOD COVERED

October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Hearing and Neomycin Therapy for Type II Hyperlipidemia**

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. A. Pikus, Audiologist, CC
Other: A. Grimes, Audiologist, CC
E. Elkins, Audiologist, CDP, NINCDS
J. Hoeg, Molecular Disease Branch, NHLBI

COOPERATING UNITS (if any)

Clinical Center Audiology
Molecular Disease Branch, NHLBI

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.30	.30	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A double-blind study of the effects of neomycin on hearing is being conducted in patients with Type II Hyperlipidemia. Patients are receiving oral neomycin and dietary regulation in rotation and/or combination. Audiologic examinations establishing baseline data are followed at predetermined increments to be related to the other study variables.

**Part of larger study on Type II Hyperlipidemia and Neomycin Therapy

PHS-6040
(Rev. 2-81)

PROJECT DESCRIPTION

Objectives: To determine whether orally administered neomycin has ototoxic effects in this population.

Methods Employed: Due to the variability of onset of symptomatic hearing loss (may be concurrent with drug or delayed for several months), baseline and frequent interim hearing evaluation are performed. Speech discrimination in ipsilateral noise is included in the test battery.

Major Findings: Several patients have been excluded from the Neomycin study after initial audiology evaluation, due to already-compromised hearing. Preliminary data is currently being gathered.

Significance to Biomedical Research and the Program of the Institute: This study relates to Goal #68 of the NINCDS National Research Strategy Report which states: Determination of the causes of acquired sensorineural hearing losses especially the effects of aging, drug ototoxicity, and environmental pollutants such as noise, in order to move toward prevention.

Proposed Course: Literature suggests neomycin is not ototoxic when administered orally, except in cases of pre-existing kidney or liver damage. However this is the first major controlled study with a large population (approximately 40 patients). Project will run 24-36 months.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02464-01 CDP

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Audiologic Findings in Autism**

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. A. Pikus, Audiologist, CC
Other: A. Grimes, Audiologist, CC
J. Rapoport, Biological Psychiatry Branch, NIMH
J. Rumsey, Biological Psychiatry Branch, NIMH
E. Elkins, Audiologist, CDP, NINCDS

COOPERATING UNITS (if any)

Clinical Center
Biological Psychiatry Branch, NIMH

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .20	PROFESSIONAL: .20	OTHER: .00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Peripheral auditory function is being evaluated in children and adults diagnosed as having Autism. For this difficult to test population, differential audiologic assessment is a prerequisite to appropriate long term educational and psychological management. Additionally, the occurrence of auditory deficits in this population has not been clearly defined.

**Part of a larger study on Brain Electrical Activity in different populations of behavioral and learning disabled.

PHS-6040
(Rev. 2-81)

PROJECT DESCRIPTION

Objectives: To evaluate peripheral auditory function in children and adults diagnosed as having autism and ascertain occurrence of auditory deficits in this population. Measures are conducted to determine the integrity of the peripheral auditory system in order to rule out hearing loss as a major factor in language delays or pathology.

Methods Employed: Traditional and behavioral techniques are employed to obtain an audiological evaluation of the peripheral mechanism. Auditory evoked potentials are being obtained by a cooperating laboratory so that correlative measures of brainstem and peripheral function can be obtained.

Major Findings: Though the study has just been initiated, some subjects are manifesting previously undiagnosed mild conductive losses, amenable to medical intervention, while others show high frequency sensorineural losses.

Significance to Biomedical Research and the Program of the Institute: Successful management of patients with multiple handicaps requires that all abnormalities be identified as early as possible.

Proposed Course: Enrollment of patients will continue and significant hearing impairment profiles will be identified as the data permit.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02465-01 CDP

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Hearing in Peripheral Neurofibromatosis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. A. Pikus, Audiologist, CC
Other: E. Elkins, Audiologist, CDP, NINCDS
A. Grimes, Audiologist, CC
J. Bader, Epidemiology Branch, NCI

COOPERATING UNITS (if any)
Clinical Neurogenetics Studies, Neuroepidemiology Section, ODIR, IRP, NINCDS
Cancer Epidemiology Branch, NCI
Clinical Center Audiology Clinic

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.10	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An interdisciplinary clinic has been staffed for the evaluation of patients with peripheral neurofibromatosis (NF) and their families. Due to the dominant inheritance pattern of the disease, the probability of involvement of offspring is 50-50. The nature and extent of auditory deficits associated with the disorder have not previously been defined in this population. This patient population is being evaluated to provide recommendations for treatment and follow-up by the referring primary-care physicians.

PROJECT DESCRIPTION

Objectives: To develop reliable techniques for the assessment of hearing disorders associated with peripheral neurofibromatosis. We are cooperating with specialists in genetics and genetic counselling, neurology, neurosurgery, orthopedics, physical medicine and rehabilitation, otolaryngology, dermatology, radiology and cancer to develop recommendations for treatment of these patients and their families.

Methods Employed: In addition to routine procedures, evoked potentials to acoustic stimuli presented through earphones are being obtained. With an active electrode placed on the vertex of the head; a reference electrode on the earlobe receiving the stimuli; and a ground electrode on the contralateral earlobe, we record responses which occur within 10 msec after click stimulation. The intensity of the signals ranges from inaudible levels up to 125 dB sound pressure level (SPL). Levels of stimuli presentation are selected for the individual subject. At no time is the subject sedated.

Major Findings: Findings of 30 NF patients suggest diverse auditory deficits and abnormal tympanometry and acoustic reflexes in approximately 60%. Positive retrocochlear findings are rare. The occurrence, type and severity of auditory deficit appears unrelated to the clinical severity assigned to each NF patient.

Significance to Biomedical Research and the Program of the Institute: This project relates to the National Research Strategy Goal #65 which states: Research on the identification and quantification of auditory function, in order that patients with hearing disorders and diseases may be properly evaluated and effectively treated.

Proposed Course: Evaluation of new patients enrolled in the protocol will continue in addition to continuous monitoring of current patients to document the relatively high incidence of auditory deficits and attempt to develop a profile of typical deviations from normal auditory performance.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02466-01 CDP

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Pediatric Oncology Regime and Ototoxicity

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.	A. Pikus, Audiologist, CC
Other:	A. Grimes, Audiologist, CC
	E. Elkins, Audiologist, CDP, NINCDS
	P. Pizzo, Pediatric Oncology Branch, NCI

COOPERATING UNITS (if any)

Clinical Center, NIH
Pediatric Oncology Branch, NCI

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .20	PROFESSIONAL: .20	OTHER: .00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

All pediatric oncology patients on the "fever" protocol are given periodic complete audiological analyses to ascertain if certain antibiotic agents used in prevention or treatment of infection have damaging effects on the patients' hearing over time.

PROJECT DESCRIPTION

Objectives: To develop sensitive indices of early ototoxic signs in a pediatric population.

Methods Employed: Complete standard battery including pure tone testing, speech reception threshold, supra-threshold speech discrimination, tolerance for speech, tympanometry and acoustic reflex studies. Experimental studies include responses to pure tones above 8 kHz and speech discrimination in ipsilateral competing noise.

Major Findings: No preliminary results at this time.

Significance to Biomedical Research and the Program of the Institute: This study relates to Goal #68 of the NINCDS National Research Strategy Report which states: Determination of the causes of acquired sensorineural hearing losses especially the effects of aging, drug ototoxicity, and environmental pollutants such as noise, in order to move toward prevention.

Proposed Course: Project will extend for 2 to 3 years.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02467-01 CDP

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Auditory Function and Cerebral Vasculitis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.	A. Pikus, Audiologist, CC
Other:	A. Grimes, Audiologist, CC
	E. Elkins, Audiologist, CDP, NINCDS
	R. Roberts, LCI, NIAID

COOPERATING UNITS (if any)

Clinical Center Audiology
Laboratory of Clinical Investigation, NIAID

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.15	.15	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This auto-immune disease is associated with auditory and vestibular symptoms. Incomplete information is available on its manifestations in the auditory system.

PROJECT DESCRIPTION

Objectives: To determine the nature and extent of auditory system involvement in this disorder.

Methods Employed: A test battery including pure tones, speech reception threshold, supra-threshold speech discrimination, tolerance for speech, tone decay and middle ear function is followed by special site-of-lesion tests to determine involvement of various portions of the auditory mechanism.

Major Findings: To date, most patients demonstrate some sensorineural loss, usually without brainstem involvement. Substantial fluctuations in peripheral hearing are being observed.

Significance to Biomedical Research and the Program of the Institute: The relationship of various disorders to impairment of the auditory mechanism needs to be documented for effective patient care.

Proposed Course: Ongoing to obtain a large enough subject population for interpretation of parametric analyses.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02468-01 CDP

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Audiologic Findings in Wegener's Granulomatosis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. A. Pikus, Audiologist, CC
Other: E. Elkins, Audiologist, CDP, NINCDS
A. Grimes, Audiologist, CC
A. Fauci, LCI, NIAID

COOPERATING UNITS (if any)
Clinical Center Audiology
Laboratory of Clinical Investigations, NIAID

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .10	PROFESSIONAL: .10	OTHER: .00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This auto-immune disease is often manifested by intractable middle ear diseases in addition to cochlear involvement. The current study evaluates the nature and extent of auditory deficits associated with Wegener's Granulomatosis to determine any effects of treatment on hearing and middle ear function.

PROJECT DESCRIPTION

Objectives: To evaluate the nature and extent of auditory system involvement during the course of this disease. Quantification of the effects of medical treatment on the multiple measures of hearing will be performed over time.

Methods Employed: Audiological evaluation includes pure tone testing, speech reception threshold, supra-threshold speech discrimination, tolerance for speech, and middle ear analyses (tympanometry and acoustic reflex studies). Speech tests are performed as indicated from the results of the above battery.

Major Findings: Fluctuating conductive hearing impairment is a prominent occurrence usually accompanied by some high-frequency sensorineural component which appears to be progressive over time.

Significance to Biomedical Research and the Program of the Institute: Research Goal #64 developed for the Institute in the National Research Strategy Plan stated the need for "Clinical research to provide needed new information for improved patient care for the hearing-impaired."

Proposed Course: To obtain serial measurements of auditory function and develop a profile of severity of deficits to determine extent of expected handicap.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02469-01 CDP

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Small Cell Carcinoma and Hearing Loss

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. A. Pikus, Audiologist, CC
Other: A. Grimes, Audiologist, CC
E. Elkins, Audiologist, CDP, NINCDS
A. Lichter, Radiation Therapy Section, NCI

COOPERATING UNITS (if any)

Clinical Center Audiology
Radiation Therapy, NIH

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .05	PROFESSIONAL: .05	OTHER: .00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Patients with Small Cell Carcinoma of the lung are often treated with chemotherapeutic agents and radiation therapy in combination or sequence. Concern has developed over hearing loss in some patients. Project is designed to help identify which (if either) factor may be causally related to hearing deficits in this patient population.

PHS-6040
(Rev. 2-81)

PROJECT DESCRIPTION

Objectives: To identify relationship, if any, of chemotherapeutic agent, radiation therapy and hearing impairment.

Methods Employed: Complete standard battery including pure tone testing, speech reception threshold, supra-threshold speech discrimination, tolerance for speech, tympanometry and acoustic reflex studies. Experimental studies include responses to pure tones above 8 kHz and speech discrimination in ipsilateral competing noise.

Major Findings: No results at this time.

Significance to Biomedical Research and the Program of the Institute: This study relates to Goal #68 of the NINCDS National Research Strategy Report which states: Determination of the causes of acquired sensorineural hearing losses especially the effects of aging, drug ototoxicity, and environmental pollutants such as noise, in order to move toward prevention.

Proposed Course: Project is expected to take 18-24 months.

TAB 4 -- FUNDAMENTAL NEUROSCIENCES PROGRAM -- FNP

ANNUAL REPORT

October 1, 1980 through September 30, 1981

Fundamental Neurosciences Program

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

INTRODUCTION 1

GENERAL FUNDAMENTAL NEUROSCIENCES

- Research Grants and Program Project Grants 1-3
- Application of Hybridoma Technology to the Nervous System 4
- Mechanisms of Learning in Simple Nervous Systems 4
- Neuroanatomical Asymmetry in the Human Temporal Lobes 5
- Neurophysiology of Cognitive Processes 5
- Integration of Autonomic and Somatic Divisions of the Nervous System 5

NEURAL PROSTHESIS 6

BIOMEDICAL ENGINEERING 6

SCIENTIFIC INFORMATION EXCHANGE

- Cooperative Activities with the National Library of Medicine 6
- The Neurosciences Research Program 7

PROGRAM ANNOUNCEMENT 8

CONTRACT NARRATIVES

- Studies of Urinary Bladder Evacuation by Electrical Stimulation NO1 NS 3-2307 9
- Transdermal Stimulation Electronics for Auditory Prostheses NO1 NS 5-2306 10
- Neuroanatomical Asymmetry in the Human Temporal Lobes and Related Psychological Characteristics NO1 NS 6-2344 11
- Development of Improved Capacitor Stimulating Electrodes NO1 NS 8-2300 12
- Development of Improved Capacitor Stimulating Electrodes NO1 NS 8-2392 13

Biomaterials for Neural Prostheses
N01 NS 8-2393 14

Biomaterials for Neural Prostheses
N01 NS 8-2394 15

Safe Procedures for Electrical Stimulation of the Nervous System
N01 NS 9-2315 16

Electrochemical Studies
N01 NS 9-2316 17

Safe Methods of Electrical Stimulation
N01 NS 0-2319 18

Study of Intramuscular Electrical Stimulation of Muscle
N01 NS 0-2330 19

Study of the Effects of Electrical Stimulation of the Cerebellum
N01 NS 0-2332 20

Transducer Development and Evaluation of Sensory Feedback
N01 NS 0-2335 21

Development of Multichannel Stimulating Electrodes
N01 NS 0-2336 22

Development of Multichannel Stimulating Electrodes
N01 NS 0-2337 23

Development of Transdermal Stimulation Electronics for an Auditory Prostheses
N01 NS 1-2354 24

ANNUAL REPORT
October 1, 1980 - September 30, 1981
Fundamental Neurosciences Program
National Institute of Neurological and
Communicative Disorders and Stroke

INTRODUCTION

Basic research in the neurosciences is supported by all four Extramural Programs. However, the Fundamental Neurosciences Program is primarily concerned with those projects which are not obviously disease-related and serve to expand the store of scholarly information in the classic disciplines of neuroanatomy, neurophysiology, neurochemistry, neuropharmacology and neuropsychology. This is the base upon which clinical research is ultimately dependent, not only for information, but for the development of instruments, techniques and methodologies which make applied research possible. The basic research laboratory not only provides the tools for clinical investigation but often the training in scientific methodology as well.

The Neural Prosthesis Program, directed by Dr. F.T. Hambrecht, is an important aspect of FNP activities. It is primarily oriented toward the study and solution of basic problems at the interface between electrodes and nervous tissue, issues which must be satisfactorily resolved before the chronic implantation of devices to compensate for lost sensory or motor capacities. These involve electrode toxicity and materials, parameters of stimulation, corrosion by body fluids, electronic pack encapsulation, and the design and construction of multiple electrodes. This program, one of the few of its kind in the world, is primarily supported through research contracts at the level of about 2.6 million dollars a year.

GENERAL FUNDAMENTAL NEUROSCIENCES

On July 13, 1981 there were 420 regular research grants and 10 program project grants in the program (see tables). About equal numbers of grants were in neurophysiology and neurochemistry. Together, they accounted for about 80% of FNP grants. Twelve percent of the regular research grants supported studies in neuroanatomy with smaller numbers of grants in other biological sciences, psychobiological relationships, neural prostheses, and biomedical engineering. Four program projects were for neurophysiological studies, three for neurochemical studies, two for neuroanatomical studies, and one for biomedical engineering. It should be noted that the program only includes those basic neuroscience grants which are not directly disease- or disorder-related and thus represents only a fraction of NINCDS support for studies of neural structure and function.

FUNDAMENTAL NEUROSCIENCES PROGRAM

ACTIVE REGULAR RESEARCH GRANTS
JULY 1981

	Number	% of Total	$	% of Total $
Neuroanatomical Sciences	51	12 %	3,235,628	11 %
Neurophysiological and Neurophysical Sciences	171	40.5%	11,689,551	40 %
Biochemical Sciences	163	39 %	11,756,962	40 %
Biological Sciences	20	5 %	1,654,421	5.5%
Psycho-Biological Relationships	8	2 %	604,044	2 %
Neural Prostheses and Biomedical Engineering	7	1.5%	391,221	1.5%
TOTALS	420	100%	29,331,827	100%

FUNDAMENTAL NEUROSCIENCES PROGRAM

ACTIVE PROGRAM PROJECT GRANTS
JULY 1981

	Number	% of Total	$	% of Total $
Neuroanatomical Sciences	2	20%	932,238	27.5%
Neurophysiological and Neurophysical Sciences	4	40%	908,844	27 %
Biochemical Sciences	3	30%	1,311,784	39 %
Biological Sciences				
Psycho-Biological Relationships				
Neural Prostheses and Biomedical Engineering	1	10%	223,736	6.5%
TOTALS	10	100%	3,376,702	100%

Application of Hybridoma Technology to the Nervous System

As in other disciplines, progress in the neurosciences follows the development of new methods and technologies that can be brought to bear on classical problems. For example, the refinement of immunocytochemical approaches stimulated a great burst of activity in the identification, localization, and physiology of the neuropeptides. This technique is based on the production of antibodies to the peptide by a suitable animal, followed by its isolation and labeling with a fluorescent or radioactive marker. The antibody, applied to a section on a slide, is bound by the tissue antigen--the peptide. This general method received a tremendous impetus with the development of hybridomas by means of which an almost unlimited supply of highly specific, monoclonal antibodies could be obtained.

Hybridoma production begins by immunizing a mouse with antigenic material and fusing the resulting lymphocytes with myeloma cells which multiply indefinitely in culture. The objective is to combine the immortality of the myeloma cells with the specific antibody production of the plasma cells. Although screening numerous hybridomas for the appropriate antibodies is an arduous task, the positive hybrids are cloned resulting in a potentially large supply of specific antibodies.

The method has been utilized for a variety of studies on nervous tissue. One very promising application involves the production of antibodies against whole leech nerve cords. By careful screening of the various hybrid products, a number of very specific antibodies has been uncovered which react with small subsets of neurons whose functions and connections have been well established. Combining information on specific antigen (e.g. protein or peptide) localization with electro-physiological and anatomical characterization, the molecular mechanisms of neural specificity and neural connectivity may be defined. In fact, each neuron may be biochemically unique. The ability of the nervous system to generate coherent behavior is dependent on vast numbers of precise connections between nerve cells. In addition, monoclonal antibodies can be injected into living cells containing the corresponding specific antigen, and the effects on function observed.

Mechanisms of Learning in Simple Nervous Systems

One of the primary goals of neuroscience is to describe behavior, such as learning and memory, in terms of biochemistry and physiology. Utilizing the relatively simple nervous systems of the Aplysia and leech, much has been learned of the "wiring diagrams", control systems, neurotransmitters, and the specificity of regenerated synapses. However, the activities observed represent, for the most part, basic reflex behavior. Learning is usually thought to involve change in behavior as a result of experience or, in one of the simplist cases, a change in synaptic characteristics as a result of previous activity. The type of behavior that neurobiologists would like to characterize in molecular terms is associative learning, i.e., the conditioned reflex. This has been demonstrated in Aplysia, but at present, little is known of the plastic neuronal, synaptic or biochemical modifications that underlie the acquisition of the conditioned reflex. However, more information is available on habituation and sensitization--two types of non-associative learning considered more primitive, but may constitute the basis of complex behavior. Habituation usually refers to decrement in response to repeated stimulation while a facilitated or augmented response is termed sensitization.

Illustrative of research in the field is the elucidation of the mechanism underlying sensitization of the gill withdrawal reflex in Aplysia. The primary sensory to motor neuron synapse is facilitated by stimulation of another specific ganglion cell. Serotonin released from the facilitator neuron acts on receptor-coupled adenylate cyclase at the sensory neuron terminal to stimulate production of cyclic adenosine monophosphate (AMP). The cyclic AMP in conjunction with a calcium regulatory protein stimulates phosphorylation of the calcium channel in the membrane via protein kinases. When phosphorylated, the calcium channel opens to admit more calcium, thus augmenting release of transmitter from the sensory neuron on the motor neuron. This cascade of biochemical steps initiated by the release of serotonin by the facilitator neuron onto terminals of sensory neurons (resulting in sensitized gill withdrawal), provides a firm basis for understanding the molecular events underlying synaptic plasticity.

Neuroanatomical Asymmetry in the Human Temporal Lobes

The investigation of neuroanatomical asymmetry in the human temporal lobes and correlated psychological characteristics continues at McMaster University. Over 72 volunteers have been given psychological tests and, despite some losses, 32 brain specimens have been obtained. Decisions have been made recently as to the histological procedures to be used on selected brains, and the gross measurements to be used for all brains. Preliminary results suggest some interesting features of the neuroanatomical asymmetry in the temporal and nearby frontal areas; some correlations with the test scores will be sought in the coming year. This unique research data should provide new clues about the nature of hemispheric specialization.

Neurophysiology of Cognitive Processes

Interest has been brisk in this Program Announcement issued in July 1980 encouraging research involving both neurophysiologists and cognitive neuroscientists in the attempt to elucidate the mechanisms of cognitive processes at the neural level. Three applications were considered at the January 1981 NANCDS Council meeting and 18 were brought to the May 1981 meeting. It is expected that interest will remain high in this difficult but important area.

Integration of Autonomic and Somatic Divisions of the Nervous System

In October 1980, FNP issued a Program Announcement "Integration of Autonomic and Somatic Divisions of the Nervous System". Stimulation of this research area was enthusiastically endorsed by the FNP Advisory Committee to remedy a long-standing, unfortunate dichotomy in neurophysiological studies. The separation of the nervous system into somatic and autonomic divisions has obfuscated and neglected their constant intimate interrelationships in support of tissue function. During FY 1981, five proposals were received of which two were funded.

NEURAL PROSTHESIS

The attached contract narratives describe recent findings from neural prosthesis projects supported by contract. The projects are interrelated, and the Principal Investigators work closely together under the coordination of the Project Officer. For example, neural tissue which has been subjected to long-term electrical stimulation by one contractor is analyzed for possible toxic metal electrode corrosion products by another contractor after being examined histopathologically by a third contractor. The electrodes used are designed and fabricated by a fourth investigator. This cooperation permits the application of state-of-the-art multidisciplinary techniques to the solution of fundamental problems which are preventing the development of aids for the neurologically handicapped.

Exciting new findings include the demonstration of the feasibility of developing artificial sensory transducers for individuals who do not have normal tactile sensation and the successful evaluation of the safety and efficacy of miniature capacitor stimulating electrodes in primates. The investigation of restoration of upper extremity movement in quadriplegic individuals has continued with the incorporation of more automatic, computer control which has reduced the conscious effort required and increased the speed of response.

BIOMEDICAL ENGINEERING

The Biomedical Engineering Program will soon include a new contract to develop and fabricate multichannel intracortical recording electrode arrays. These electrodes should permit simultaneous recording of single unit activity from multiple sites within a single cortical column. Since microelectronic photolithography will be used, a high degree of accuracy in electrode size and position will be possible. The cost of these electrodes also promises to be low compared to hand-fabricated electrodes. Another contract for the development of transdermal stimulators has been in a production phase with the first of twenty-five operational eight-channel stimulators being completed. A new design with regulated current output stages is now being initiated. A program project grant that involves the design and fabrication of custom instruments for neuroscience research was renewed this year. Unfortunately, FNP staff had to request that the applicant make a reduction in the level of effort so that enough money would be available to continue other meritorious grants. This was in addition to reductions suggested by the initial review group.

SCIENTIFIC INFORMATION EXCHANGE

Cooperative Activites with the National Library of Medicine

At the 1980 Society of Neuroscience Annual Meeting, the Fundamental Neurosciences Program (FNP), in cooperation with the National Library of Medicine (NLM), exhibited the stored-search system offered by NLM, and the search strategies on neuroscience topics prepared by FNP. There was considerable interest by neuroscientists in the stored-search capability at the NLM and in the search strategies that facilitated use of this capability. In 1979, the FNP prepared search strategies on eight neuroscience topics: sleep, neurochemical transmitters, peptides, the pituitary gland, the endocrine system, neuroimmunology, cerebral evoked potentials, and developmental neurobiology. These strategies were updated for the 1980 meeting. They are intended to assist neuroscientists in working with their medical librarians to develop customized search strategies on neuroscience subjects that can be stored on the NLM system to yield automatic monthly bulletins as a current alerting service to the individual scientist.

The favorable response at the two annual meetings of the Society for Neuroscience prompted the FNP to distribute copies of the search strategies and the descriptive material on the services available at the NLM to its grantees. This distribution exhausted the supply of printed materials and marked a termination point in our effort to direct neuroscientists toward available information sources.

The Neurosciences Research Program

The Neurosciences Research Program (NRP), currently part of the Massachusetts Institute of Technology, organizes, implements, and publishes the results of a program of international interdisciplinary collaboration by leading experts on conceptual problems at all levels of organization of the nervous system--molecular, cellular, neural and behavioral. The primary goals of this collaborative conceptual research are:

1. To evaluate data -- what is well established, what is controversial, and what is unknown;

2. To cast the available information in new conceptual perspectives, especially those bridging across disciplinary barriers;

3. To formulate expert opinions on directions and methods for future experimental analysis; and

4. Ultimately, to develop a scientific understanding of the role of neurobiological processes in behavior, including human cognitive processes.

After August 1982, NRP will continue its program under the auspices of the Rockefeller University and the leadership of G.M. Edelman and Vernon Mountcastle.

PROGRAM ANNOUNCEMENT

The FNP issued the following Program Announcement in the October 10, 1980 issue of the NIH Guide for Grants and Contracts:

Integration of Autonomic and Somatic Divisions of the Nervous System

The Fundamental Neurosciences Program (FNP) of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) encourages the submission of applications for research grants for the investigation of somatic-autonomic mechanisms of neuronal integration. Emphasis is placed on the effects of 1) "visceral afferents" on higher nervous processes and 2) cutaneous stimulation on autonomic activity.

BACKGROUND

The common classification of nerve fibers as visceral or somatic afferent and visceral or somatic efferent, and the separation of the nervous system into somatic and autonomic divisions, have obfuscated their intimate interrelationships in support of tissue function. Somatic activity is almost always accompanied by reactions involving the autonomic nervous system such as vascular adjustments accompanying muscular contraction. The activity of autonomically innervated organs influence diverse central nervous system structures, via visceral afferent pathways.

EXAMPLES

Projects of the following types illustrate this area:

1. Baroreceptor and chemoreceptor ("visceral afferent") influences on cortical activity. Several studies suggest that baroreceptor stimulation is accompanied by changes in cortical activity which may influence non-cardiovascular activities, detectable physiologically and behaviorally.

2. Effects of cutaneous stimulation on autonomic activity (somato-autonomic reflexes). Stimulation of sensory receptors in the skin may be accompanied not only by cardiovascular responses but by changes in the bladder, stomach, or intestines through visceromotor activation.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1980 through September 30, 1981

Contractor: UNIVERSITY OF CALIFORNIA, SAN FRANCISCO (N01-NS-3-2307)

Title: Studies of Urinary Bladder Evacuation by Electrical Stimulation

Contractor's Project Director: Emil Tanagho, M.D.

Current Annual Level of Support: $112,516

Objectives: Studies are being conducted in animals with upper motor neuron lesions to determine the feasibility of urinary bladder evacuation by electrical stimulation of the sacral spinal roots. Studies are also being carried out on methods of preventing urinary incontinence.

Major Findings: Prior to human implants, successful animal testing is required of the bladder evacuation system. The last of five animals implanted, three of which have had spinal cord sections at the lumbar level, have shown no changes in bladder evacuation threshold and no equipment failures. These animals range from seven months to four months post implant. In animals that have not had selective somatic rhizotomies, the tail muscles are stimulated in addition to the urinary and anal sphincters. After two months of stimulation, significant hypertrophy of the muscles at the base of the tail occurs. Studies of the histochemical properties of the urethral sphincter in dogs as a function of distance from the bladder has been completed. The percentage of fast contracting, fatigue sensitive, glycolytic fibers increases relative to the percentage of slow contracting, fatigue resistant oxidative fibers as one sections the urethra from bladder to outlet.

Significance to Biomedical Research and to the Program of the Institute: The restoration of the ability of persons with neurogenic bladders to empty their bladders voluntarily is a long-range goal of this work and would reduce urinary tract infections that are a major cause of death in paraplegics and quadriplegics. The problem of urinary incontinence is of both social and medical significance, especially in the geriatric population.

Proposed Course of Contract: This contract will terminate in December 1981. A new RFP (RFP 81-13) has been released and is designed to allow clinical evaluation of the techniques developed under this contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1980 through September 30, 1981

Contractor: STANFORD UNIVERSITY (N01-NS-5-2306)

Title: Transdermal Stimulation Electronics for Auditory Prostheses

Contractor's Project Director: Robert L. White, Ph.D.

Current Annual Level of Support: $0

Objectives: Design, development, and fabrication of transdermal stimulators to be used in the evaluation of multichannel cochlear implant auditory prostheses.

Major Findings: (1) Sixty bipolar chips, 60 logic chips, and 120 gate chips have been fabricated and sent to an external vendor for packaging of 25 STIMULISS VIIIA receiver-stimulators. (2) The next generation eight-channel current controlled system is proceeding on schedule. (3) A new type of detector has been designed which consumes 1/100 of the power of the present envelope detector. (4) A computer simulation of a depletion mode current gate is presently underway to improve fabrication reliability.

Significance to Biomedical Research and to the Program of the Institute: The Institute is presently supporting, under the grants mechanism, the evaluation of multichannel auditory prostheses. This contract will provide electronic stimulators to several of these grantees.

Proposed Course of Contract: This contract expired on June 30, 1981. The workscope was advertised for competitive bids and the winning proposal was from Stanford University. The new contract number is N01-NS-1-2354.

.CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1980 - September 30, 1981

Contractor: McMASTER UNIVERSITY (NO1-NS-6-2344)

Title: Neuroanatomical Asymmetry in the Human Temporal Lobes and Related Psychological Characteristics

Contractor's Project Director: Sandra F. Witelson, Ph.D.

Current Annual Level of Support: $51,000

Objectives: Patients in good neurological and mental health at a cancer clinic are approached by a trained "clinical coordinator" about granting permission for autopsy and taking psychological tests. The tests are those demonstrated to be affected by cerebral lesions of the temporal lobe on the left or right; certain variations in anatomical asymmetry in the two normal temporal lobes will be investigated for relationships to the test scores.

Major Findings: As of June, 71 patients signed consent forms, and have undergone some testing. Some brains are not obtained; 31 specimens have become available. New histological procedures have been developed with Dr. Marc Colonnier, for the analysis of selected brains.

Significance to Biomedical Research and to the Program of the Institute: The research bids well to help solve a basic question of why nearly a quarter of human brains do not show the temporal lobe asymmetry of the two-thirds majority; the results should provide some insight into the nature of the hemispheric specialization of the human brain.

Proposed Course of Contract: Testing of patients is expected to continue until February 1982 before the funding expires; two extensions have been granted, and another will be applied for (expenses were less than originally expected, in part as a result of the devaluation of the Canadian dollar). The histological analysis of some brains with extreme gross asymmetry in the temporal area should be completed soon.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1980 through September 30, 1981

Contractor: GINER, INC. (N01-NS-8-2300)

Title: Development of Improved Capacitor Stimulating Electrodes

Contractor's Project Director: Harry Lerner, Ph.D.

Current Annual Level of Support: $0

Objectives: Research on methods of increasing the charge storage capability per unit volume and the current density output capability of capacitor electrodes that are suitable for stimulation of neural tissue is being carried out.

Major Findings: (1) The feasibility of preparing porous sintered titanium electrodes as well as electrolytically etched electrodes was demonstrated. These electrodes have higher charge storage densities than comparable sized tantalum electrodes but their leakage currents were about 2 orders of magnitude greater. (2) As in the case of tantalum electrodes, pulse anodization of titanium significantly increases the capacitance compared to direct current anodization. (3) Attempts to make tantalum electrodes of 100 microns diameter using the glycerin slurry technique has been unsuccessful due to difficulty masking the active tips and preventing the slurry droplet from moving up the conically shaped shaft.

Significance to Biomedical Research and to the Program of the Institute: The capacitor stimulating electrode is the safest method presently available to stimulate neural tissue. Improvement in its stimulating capabilities and methods of reducing its physical size will permit the development of more sophisticated and safer neural prostheses which utilize stimulation of central nervous system tissue.

Proposed Course of Contract: This contract will terminate in September 1981.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1980 through September 30, 1981

Contractor: EIC CORPORATION (N01-NS-8-2392)

Title: Development of Improved Capacitor Stimulating Electrodes

Contractor's Project Director: Barry Brummer, Ph.D.

Current Annual Level of Support: $0

Objectives: Improvements in the charge storage capability per unit volume and the current density output capability of capacitor electrodes suitable for intracortical stimulation of neural tissue are the major objectives. Prototype capacitor electrodes will be fabricated and supplied to other investigators.

Major Findings: (1) Titanium dioxide films with a dielectric constant of 79±20 have been formed on titanium wires. This is more than twice the dielectric constant of tantalum pentoxide. However, the best titanium capacitor electrodes that have been fabricated to date, have a charge storage capability of only about one-half to one-third that of the best tantalum electrodes with comparable leakage currents. (2) Barium titinate films 550 to 1500 angstroms thick have been sputtered onto titanium wires. These films have relatively large leakage currents with effective resistivities of 2×10^{10} ohm-cm. The capacitance of .28 microfarad/mm^2 was measured for the 1600 angstrom film which corresponds to a dielectric constant of about 500.

Significance to Biomedical Research and to the Program of the Institute: The capacitor stimulating electrode is the safest method presently available to stimulate neural tissue. Improvement in its stimulating capabilities and methods of reducing its physical size will permit the development of more sophisticated and safer neural prostheses which utilize stimulation of neural tissue.

Proposed Course of Contract: This contract will terminate in September 1981.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1980 through September 30, 1981

Contractor: UNIVERSITY OF MISSOURI (N01-NS-8-2393)

Title: Biomaterials for Neural Prostheses

Contractor's Project Director: Allen Hahn, Ph.D.

Current Annual Level of Support: $0

Objectives: Development of new biomaterials for use as implant encapsulants, primers, and lead insulators.

Major Findings: (1) When synthesizing Parylene-C, the use of argon gas to increase system pressure tends to degrade the mechanical properties of the Parylene. This does not appear to be true when synthesizing Parylene-N. (2) Biocompatibility studies indicate that Parylene-N is associated with gliosis and fibrotic reaction when used on cortical implants. (3) Measurements of electrical properties of Parylene-C synthesized in the glow-discharge chamber are of the same order of magnitude as those reported by Union Carbide. The same is true of measurements of vapor transport through "free-standing" films.

Significance to Biomedical Research and to the Program of the Institute: Many implanted devices that are presently available or are planned for the future are adversely affected by water and sodium ions in extracellular fluid. Development of improved encapsulation and sealing systems to prevent their access to the implants will be useful not only to neural prostheses, but to other artificial organs that involve implanted electronics.

Proposed Course of Contract: This contract will terminate in September 1981.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1980 through September 30, 1981

Contractor: CITY UNIVERSITY, LONDON (N01-NS-8-2394)

Title: Biomaterials for Neural Prostheses

Contractor's Project Director: Mr. Keith Allen

Current Annual Level of Support: $0

Objectives: Improvement of the adhesion of insulators to conductors and other insulators that are used as implant packages, encapsulants, sealants and lead insulators in implanted neural prostheses.

Major Findings: (1) The hydrolysis of silicone rubber (DC 3140) in water at five different temperatures has been determined over a period of 57 days. If these rates continue, one would expect about a 6 percent failure rate over a period of about 20 years. (2) A surface pretreatment has been developed which improves the adhesion of silicones to tantalum. (3) Silane primers significantly improve the adhesion of silicone rubbers to both alumina substrates and tantalum substrates. At the present time, there are no medical grade Silane primers. (4) Some silicone rubbers are slow to cure in thin films when exposed to air even though they achieve good cures when used in bulk form. (5) Following surface pretreatment, immersion of tantalum substrates in boiling water increases the adhesive bond strengths to silicones. (6) Heating of tantalum substrates to about 250°C improves bond strengths by about 30 percent compared to room temperature samples.

Significance to Biomedical Research and to the Program of the Institute: Many implanted devices that are presently available or are planned for the future are adversely affected by water and sodium ions in extracellular fluid. Development of improved sealing systems to prevent access of water and sodium ions to the implants will be useful not only to neural prostheses, but to all artificial organs that involve implanted electronics.

Proposed Course of Contract: This contract will be terminated in September 1981.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1980 through September 30, 1981

Contractor: EIC CORPORATION (N01-NS-9-2315)

Title: Safe Procedures for Electrical Stimulation of the Nervous System

Contractor's Project Director: Barry Brummer, Ph.D.

Current Annual Level of Support: $45,780

Objectives: The electrochemical processes that occur at the electrode-electrolyte interface and methods of reducing undesirable reactions are being studied.

Major Findings: (1) Glow-discharge deposited methane is not an effective inhibitor of electrode dissolution during pulsing. (2) Tissue samples from frog spinal cord which was stimulated through a platinum-10 percent iridium electrode supplied by Huntington Institute contained no detectable platinum or iridium when analyzed by flameless atomic absorption spectrophotometry with detection limits for platinum of 4 nanograms or greater and for iridium of 19 nanograms or greater. (3) Pure iridium electrodes show a progressive increase in charge capacity in the potential region where oxide species are formed. This "activation" of the iridium surface is due to the irreversible formation of oxide species above 1.4 volts versus reversible hydrogen electrodes (RHE). (4) The anodic and cathodic gassing limits for iridium microelectrodes (geometric area approximately $1 \times 10^{-6} \text{cm}^2$) are about 1000 to 1500 $\text{microcoulombs/cm}^2$ per half pulse. The major reason for this high bubbling limit is the excellent out-diffusion of dissolved gases away from the microelectrode thus avoiding supersaturation and bubble formation. Because of the difference in size between these iridium electrodes and previously tested platinum electrodes, the conclusion cannot be made that iridium has a higher gassing limit than platinum.

Significance to Biomedical Research and to the Program of the Institute: Development and evaluation of safe stimulating techniques for use in neural prostheses are major goals of the Neural Prosthesis Program of the Institute.

Proposed Course of Contract: This work is in the second year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1980 through September 30, 1981

Contractor: ELECTROCHEMICAL TECHNOLOGY CORPORATION (N01-NS-9-2316)

Title: Electrochemical Studies

Contractor's Project Director: Dr. Theodore Beck

Current Annual Level of Support: $113,664

Objectives: New stimulation electrodes based on ion selective membranes are being developed and fabricated.

Major Findings: (1) A mathematical analysis was made of practical operational modes for a system consisting of a silver-silver chloride electrode coated with a thin anion-conducting membrane to prevent silver ions from contacting body tissue. This analysis has indicated that any hydrogen developed at the electrode surface should not cause problems because it would be easily transported through the membrane and away through the surrounding body tissue. Both pure MAPTAC and pure DMAPMA have been rejected as ion exchange membranes because of loss of mechanical strength due to swelling when placed in water. Cross-linking agents are being investigated to reduce this swelling. (2) Electrodes have been fabricated with a commercial membrane, RAI P-1040. One of these electrodes is being cycled in saline and has shown a predicted daily increase in access resistance because of an excess positive charge in the biphasic pulse pair. An identical electrode with an excess cathodal charge has been cycled for 44 days with essentially no change in resistance. This is in agreement with expectations.

Significance to Biomedical Research and to the Program of the Institute: Neural prostheses that utilize functional electrical stimulation require safe techniques for long-term neuronal activation and inhibition. This work will provide a better understanding of the electrochemical factors involved and will develop new electrodes based on these findings.

Proposed Course of Contract: This contract began in January 1980 and will continue for at least one more year.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1980 through September 30, 1981

Contractor: HUNTINGTON INSTITUTE OF APPLIED MEDICAL RESEARCH (N01-NS-0-2319)

Title: Safe Methods of Electrical Stimulation

Contractor's Project Director: William Agnew, Ph.D.

Current Annual Level of Support: $203,809

Objectives: The histopathological effects of long-term electrical stimulation of the nervous system in animals are being studied with various electrode designs, stimulus wave forms, and stimulus parameters. Major emphasis is on intracortical electrodes and peripheral nerve stimulating electrodes. During stimulation, ion-sensitive electrodes are used to monitor changes in extracellular ion concentrations. When long-term stimulation is completed, the tissues surrounding the electrodes are examined using both light and electron microscopy.

Major Findings: (1) Sacral nerve roots stimulated through a new type of spiral electrode for periods up to two and one-half months show no evidence of nerve damage and only minimal connective tissue buildup. (2) The hazards of solid Silastic backing for surface electrode arrays compared to perforated Dacron were further established during the autopsy of a cat with a four-year solid, Silastic cortical surface implant which was found to have migrated intracortically to assume a vertical position. (3) A real-time automated data acquisition system has been completed which will be used in conjunction with the evaluation of stimulus parameters during nerve damage studies. (4) Long-term follow-up of animals implanted with Dacron mesh arrays on the surface of the cerebral cortex for two and one-half years show no herniation or incorporation of the Dacron mesh arrays into the brain and no behavioral changes in the animals. One animal with a Silastic array which had migrated to the vertical position was easily handled until approximately six months prior to sacrifice, after which time it exhibited aggressive and unpredictable behavior and when picked up, all four legs would extend and become rigid. It is assumed, but not proven, that these behavioral and neurological changes are due to the movement of the electrode array through the cerebral cortex. (5) A new method for fabricating intracortical microelectrodes for neural damage studies has been developed. Features include beveled tips and epoxylite insulation. Three of these electrodes can be molded together to provide an array with interelectrode spacing of 2 mm.

Significance to Biomedical Research and to the Program of the Institute: These studies are important for determining the safety and efficacy of various forms of neural stimulation utilized in neural prostheses for the neurologically handicapped. In addition, new surgical and neurophysiological techniques are being developed which are proving valuable to neurosurgeons and neurophysiologists in other laboratories and clinics.

Proposed Course of Contract: This contract began in January 1980 and will extend for at least one more year.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1979 through September 30, 1980

Contractor: CASE WESTERN RESERVE UNIVERSITY (N01-NS-0-2330)

Title: Study of Intramuscular Electrical Stimulation of Muscle

Contractor's Project Director: J. Thomas Mortimer, Ph.D.

Current Annual Level of Support: $246,000

Objectives: The use of electrical stimulation of the neuromuscular system in animals and humans for artificial control of muscle and generation of purposeful movements is being studied. The ultimate goal is to restore function to the upper extremities in patients paralyzed as the result of spinal cord injuries.

Major Findings: (1) The command controller has been interfaced directly to the laboratory stimulator and the combination evaluated directly on outpatient subjects. The system is preferable to myoelectric control because the output can be controlled more rapidly and the system is easier to don. (2) A computer-controlled system for laboratory development of elbow position control was completed. The program accepts an analog input as the control source and modulates the output stimulus pulse width and interpulse interval. (3) A mathematical model of closed-loop force feedback for control of stimulated skeletal muscle has been developed. Future models must take into account the nonlinear nature of the recruitment characteristics of muscle during electrical stimulation. (4) Test apparatus for flex testing new electrodes and lead systems has been completed. (5) Threshold differences between nerve fibers of differing diameters can be enhanced by stimulating with narrow, biphasic pulses. This effect was predicted with a computer model and varified in animal experiments. (6) An algorithm has been developed for preprogrammed control of grasp in which the thumb abductor pollicus is stimulated prior to activation of the finger flexor muscles. This relieves the human subject of conscious control of this coordinated pair of movements. (7) A nine-channel, computer controlled stimulation program has been written and is undergoing initial testing. (8) In C-6 patients, wrist motion was investigated as a command signal for key grasp. This system forms an augmented tenodesis grip. (9) A force sensor assembly has been designed based upon silicon piezoresistive strain gauge transducers. There is some pressure drift with time, but it is felt that long-term baseline stability will not be a critical factor. However, temperature characteristics are not ideal, and a form of temperature compensation may be necessary. (10) A sensor has been developed to detect thumb position. (11) Test results on very fine filament-stranded wire electrodes indicate that decoiling multistrand coiled wire through stretching may accelerate lead failure.

Significance to Biomedical Research and to the Program of the Institute: The techniques being investigated are restoring lost function to paralyzed individuals.

Proposed Course of Contract: This is the second year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1980 through September 30, 1981

Contractor: UNIVERSITY OF MINNESOTA (N01-NS-0-2332)

Title: Study of the Effects of Electrical Stimulation of the Cerebellum

Contractor's Project Director: Dr. James Bloedel

Current Annual Level of Support: $122,756

Objectives: The effects of cerebellar stimulation on primate models of spasticity and movement disorders are being evaluated. The neurophysiological mechanisms and anatomical pathways associated with such effects are being examined.

Major Findings: (1) The size of cerebellar surface stimulating electrodes has been reduced from 1.2 mm to 350 microns in diameter. With this change, specific alterations in segmental stretch reflexes and the responses of dorsal horn neurons to cutaneous stimulation have been seen during stimulation periods. For example, small changes in electrode position can result in the reflex response of the anterior tibial muscle being augmented or suppressed. (2) Cerebellar hemispheral stimulation has a greater effect on the activity and responses of dorsal horn neurons than stimulating the cerebellar vermis. (3) The effects produced by stimulating the surface of the cerebellum on stretch reflexes of the gastrocnemius-soleus and the anterior tibial muscles can be well localized. (4) Stimulation in one location on the cerebellar surface does not always produce the same reflex changes in all animals. (5) Stimulating discrete regions of the cerebellar surface can produce selective effects on different components of the stretch reflex. (6) Electrode polarity and stimulus parameters are extremely important in determining the precise effect of cerebellar stimulation on the stretch reflex. Huntington Institute's finding that Dacron mesh electrodes do not become imbedded in brain tissue has been confirmed with cerebellar surface electrodes.

Significance to Biomedical Research and to the Program of the Institute: These studies should provide information on the neurophysiological mechanisms, if any, by which cerebellar stimulation modifies normal movement and movement disorders.

Proposed Course of Contract: This investigation is in the first year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1980 through September 30, 1981

Contractor: UNIVERSITY OF UTAH RESEARCH INSTITUTE (N01-NS-0-2335)

Title: Transducer Development and Evaluation of Sensory Feedback

Contractor's Project Director: Andrew A. Schoenberg, Ph.D.

Current Annual Level of Support: $230,881

Objectives: The possibility of providing artificial pressure, force, slip and position information to quadriplegic patients has not been explored because of a lack of suitable transducers. This research will develop such transducer systems and evaluate them in a simulated model of a paralyzed hand that is controlled by functional neuromuscular stimulation.

Major Findings: 1. Prototype transducers have been fabricated with polyvinylidene fluoride (PVF), a piezoelectric polymer, with vapor deposited metal electrical contacts. The ideal combination of good adhesion and resistance to cracking on flexion has not yet been achieved. The prototype transducers, acting as proximity detectors, can indicate the presence of well-defined objects such as a drinking glass at a distance of about five inches. Slip detection is based on detecting the high frequency signals that are generated when an object slides across the fingertip transducer. The signal is easy to obtain with a good signal to noise ratio but difficult to interpret due to the effects of different surface textures. Equipment has been custom fabricated to calibrate the dynamic sensitivity of the transducers and to stretch PVF material at elevated temperature during its conversion to a piezoelectric polymer.

Significance to Biomedical Research and to the Program of the Institute: This research is part of a multidisciplinary approach to the restoration of lost function in paralyzed individuals. Restoration of sensation could also be useful to individuals with congenital absence of sensation or with severe burns.

Proposed Course of Contract: This work is in the first year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1980 through September 30, 1981

Contractor: STANFORD UNIVERSITY (N01-NS-0-2336)

Title: Development of Multichannel Stimulating Electrodes

Contractor's Project Director: Robert White, Ph.D.

Current Annual Level of Support: $190,850

Objectives: State-of-the-art microelectronic techniques are being applied to the design and development of second generation multielectrode arrays for stimulation of the eighth nerve. These electrodes will be used for the evaluation of the feasibility of multichannel auditory prostheses.

Major Findings: A problem with flexible electrode arrays that are inserted into the cochlea is damage to the basilar membrane. Early designs buckled during insertion and stuck to the walls of the scala tympani presumably because of surface tension effects. The latest design consists of a molded silicone backing in the shape of the scala on which the flexible, thin-film electrode is attached. The silicone not only prevents buckling, but due to its hydrophobic surface properties does not show the surface tension effects previously mentioned. Electrodes have been inserted to about the second turn of the cochlea.

Significance to Biomedical Research and to the Program of the Institute: Multichannel electrode arrays for stimulation of the eighth nerve may provide a means of communication for sensory deaf individuals. The NINCDS is committed to determining the feasibility of auditory prostheses for the deaf.

Proposed Course of Contract: This investigation is in the first year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1980 through September 30, 1981

Contractor: UNIVERSITY OF CALIFORNIA, SAN FRANCISCO (N01-NS-0-2337)

Title: Development of Multichannel Stimulating Electrodes

Contractor's Project Director: Michael Merzenich, Ph.D.

Current Annual Level of Support: $166,635

Objectives: The electrical and mechanical properties of the scala tympani are being studied and on the basis of these results, multichannel stimulation electrode arrays are being developed which are suitable for stimulation of the eighth nerve in humans.

Major Findings: Prototype multichannel electrodes have been fabricated with up to five pairs of electrodes. Problems have been encountered with air bubbles trapped in the structure, poor adhesion of individual segments, and poor mechanical properties on bending of the array. A new percutaneous plug has been designed and successfully tested in animals.

Significance to Biomedical Research and to the Program of the Institute: Multichannel electrode arrays for stimulation of the eighth nerve in the scala tympani may provide a means of communication for sensory deaf individuals. This Institute is committed to determining the feasibility of auditory prostheses for the deaf.

Proposed Course of Contract: This investigation is in the first year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1980 through September 30, 1981

Contractor: STANFORD UNIVERSITY (N01-NS-1-2354)

Title: Development of Transdermal Stimulation Electronics
for an Auditory Prosthesis

Contractor's Project Director: Robert L. White, Ph.D.

Current Annual Level of Support: $209,400

Objectives: Design, development, and fabrication of transdermal stimulators to be used in the evaluation of multichannel cochlear implant auditory prostheses.

Major Findings: See previous project N01-NS-5-2306.

Significance to Biomedical Research and to the Program of the Institute: The Institute is presently supporting, under the grant mechanism, the evaluation of multichannel auditory prostheses. This contract will provide electronic stimulators to several of these grantees.

Proposed Course of Contract: This contract continues the work of a previous contract and began July 1, 1981. It will continue for three years.

TAB 5 -- NEUROLOGICAL DISORDERS PROGRAM -- NDP

ANNUAL REPORT

October 1, 1980 through September 30, 1981

Neurological Disorders Program
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ORGANIZATION OF REPORT 1

PROGRAM SUMMARY STATEMENT 1

REPORT OF THE OFFICE OF THE DIRECTOR

Extramural Grants Activities

Demyelinating and Sclerosing Disorders 6
Infectious Diseases of the Nervous System 25
Muscular and Neuromuscular Disorders 35
Neurological Disorders of Aging 42
Other Neurological Studies 59

Contract Narrative

Establishment of a Research Roster for Huntington's Disease Patients and Families NO1-NS-9-2320 96

Research Project

Selected Maternal Risk Factors and Congenital Cardiovascular Anomalies Z01 NS 01163-19 NDP 4

REPORT OF THE EPILEPSY BRANCH TAB 5.A

REPORT OF THE DEVELOPMENTAL NEUROLOGY BRANCH TAB 5.B

ANNUAL REPORT
October 1, 1980 - September 30, 1981

NEUROLOGICAL DISORDERS PROGRAM
NATIONAL INSTITUTE OF NEUROLOGICAL
AND COMMUNICATIVE DISORDERS AND STROKE
NATIONAL INSTITUTES OF HEALTH

ORGANIZATION OF REPORT

The Annual Report has four sections. The first section is a brief administrative summary of the program. The second section is a report from the Office of the Director, NDP with nine subsections. The third and fourth sections are reports from the Epilepsy and Developmental Neurology Branches respectively.

PROGRAM SUMMARY STATEMENT

The Neurological Disorders Program (NDP) of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) consists of the Office of the Director, the Developmental Neurology Branch and the Epilepsy Branch. The Program has responsibility for the support of research directly or indirectly related to all of the medical neurological disorders except for stroke. The nine categories into which these disorders are grouped for administrative purposes are as follows:

Convulsive and Related Paroxsymal Disorders
(administered within the Epilepsy Branch)
Demyelinating and Sclerosing Disorders
Infectious Diseases of the Nervous System
Muscular and Neuromuscular Disorders
Neural Aspects of Learning and Behavior
Neurological Disorders of Aging
Other Neurological Studies
Neurological Disorders of Early Life
(administered within the Developmental Neurology Branch)

Grant Activity

The major mechanism of Program support is the investigator initiated research grant application. During FY 1981, the Program initiated five program announcements designed to encourage research in areas where it was felt that additional effort was appropriate.

Four of the announcements were to strengthen further the Program's emphasis on neurological disorders of the pediatric age group; i.e., Neonatal Brain Disorders, Neurological Abnormalities associated with Learning Disorders, Neural Tube Defects, and Neonatal Brain Disorders.

The Program's interest in neurological disorders of aging was emphasized with a Program Announcement specifically aimed at encouraging studies of Alzheimer's Disease, one of the presenile dementias, which complemented prior Program Announcements in FY 1980 on motor neuron diseases and movement disorders. The Program has made a deliberate effort to collaborate with other Institutes in major research initiatives. To accomplish this goal, the announcement in Alzheimer's Disease was published jointly with the National Institute on Aging.

The conversion of the support mechanism from contract to grant for the Comprehensive Epilepsy Programs has been completed. One grant was made in FY 1980; and one in FY 1981.

Highlights of grant supported research findings are presented in the subsections of the reports of Office of the Director and the Branches.

Contract Activity

The bulk of the Program's contract funds are used by the Epilepsy Branch to support their continuing program to develop more effective anti-epileptic drugs. Promising compounds are moving through the Epilepsy Branch's Chronic Toxicity Screening Program. A Request for Proposals (RFP) for an initial phase I and phase II clinical trial of anti-convulsive agents for intractable complex partial seizures, the most common cause of presently untreatable seizures in adults, will be implemented in FY 1981. These activities are described more fully in the report of the Epilepsy Branch.

The analysis and publication of the National Collaborative Perinatal Project (NCPP) data by the Developmental Neurology Branch nears completion with the publication of one monograph and numerous articles in FY 1981. Microfilming of the original NCPP data records has been completed, and transfer of the records to Federal archival storage has begun. An RFP has been issued to create a users guide so that interested members of the general biomedical public may have free access to the original data.A contract was awarded in FY 81 to study the effect of phenobarbital on cognative development in young children. This drug is widely used as prophylaxis against febrile seiqures but its long terms effects on the immature nervous system are unknown. These activities are more fully described in the report of the Developmental Neurology Branch.

Direct Operation Activities in FY 1981

1) Program Advisory Committee

The Neurological Disorders Program has an Ad Hoc Advisory Committee of outside experts to provide guidance for its activities. The Committee members are:

Robert G. Grossman, M.D.	Baylor College of Medicine
Robert J. Gumnit, M.D.	St. Paul-Ramsey Medical Center
Richard T. Johnson, M.D.	The Johns Hopkins University
Seymour Levine, M.D.	New York Medical College
Joseph B. Martin, M.D., Ph.D.	Massachusetts General Hospital
Dominick P. Purpura, M.D.	Albert Einstein College
J. Murdoch Ritchie, Ph.D., F.R.S.	Yale University
Joseph J. Volpe, M.D.	St. Louis Children's Hospital

Two meetings were held in FY 1981.

2) Voluntary Workshops

In FY 1980, the Neurological Disorders Program initiated a series of workshops with voluntary health agencies whose interests are in the area of responsibility of the Neurological Disorders Program. The last three workshops were held in FY 1981 to complete the cycle of inviting some 60-70 voluntary health agencies to Bethesda. Efforts are made to group voluntaries with similar interests at each of the workshops. These workshops have been particularly valuable in two areas: (1) the Program becomes informed of the activities of the voluntaries, particularly the research activities which they support; (2) the voluntaries become familiar with the procedures by which NINCDS provides research support, and the general areas of research support and types of award mechanisms available.

The dates of meetings and the attendees were as follows:

November 20-21, 1980
- National Genetics Foundation, Inc.
- National Tay-Sachs & Allied Diseases Association, Inc.
- National Neurofibromatosis Foundation
- The March of Dimes Birth Defects Foundation
- Children's Brain Diseases Foundation
- Dystonia Medical Research Foundation
- International Joseph Diseases Foundation, Inc.

March 16-17, 1981
- Rehabilitation International USA
- National Association for Retarded Citizens
- National Society for Autistic Children
- United Cerebral Palsy Association, Inc.
- Epilepsy Foundation of America
- National Tuberous Sclerosis Association
- Tuberous Sclerosis Association of America
- The Orton Society, Inc.

June 1-2, 1981
- Alzheimer's Disease & Related Disorders Association
- National Ataxia Foundation
- Friedreich's Ataxia Group in America, Inc.
- National Parkinson Foundation, Inc.
- Parkinson's Disease Foundation
- American Parkinson Disease Association, Inc.
- The Juvenile Diabetes Foundation

3) NDP Sponsored Workshops and Conferences

In addition to several workshops and conferences for which the Neurological Disorders Program provided financial support by the grant mechanism, the Program also provided substantial staff input into organizing and conducting a consensus meeting on Febrile Seizures in FY 1981. Program staff also helped organize and edit the Proceedings of a Conference on Neurosecretion and Brain Peptides.

4) Study of Huntington's disease in Venezuela

In March 1981, the Program sponsored a field trip to Maracaibo, Venezuela, in order to obtain family histories as well as tissue samples from several families with Huntington's disease. This focus of Huntington's disease in Venezuela is unique because all of the family members are known to be descended from a single individual with the disease. Two fairly complete geneologies were constructed, and about 120 tissue samples were returned to the United States for storage at the Massachusetts General Hospital and the Camden National Repository. This project is described further in the "Neurological Disorders of Aging" report.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 01163-19 NDP

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Selected Maternal Risk Factors and Congenital Cardiovascular Anomalies

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Bajda	Medical Consultant	OD, NDP, NINCDS
OTHER:	A. Naylor	Research Geneticist	DNB, NDP, NINCDS

COOPERATING UNITS (if any)

Birth Defects and Genetic Disorders Section, DNB, NDP, NINCDS

LAB/BRANCH
Office of the Director, Neurological Disorders Program, NINCDS

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	.5

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study, using data from the NINCDS Collaborative Perinatal Project, investigates the relation of selected factors which may affect the mothers during pregnancy, and possibly cause congenital heart defects in the children. Observations on about 47,000 pregnancy records provide case and control data for analysis. Some 486 children have been identified as having definite congenital cardiac anomalies. These include cardiac conditions which are part of known syndromes but exclude children suspected of having ventricular septal defect who are reported without cardiac defect at the 1-year examination and thereafter. Pre-selected maternal risk factors noted in the pregnancy records for the mothers of 392 children with definitely defined congenital heart anomalies are compared with control data matched for maternal age, race, date of LMP, and geographical location (institution).

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: Primary objective is the identification of maternal/enviromental conditions causing pregnancy outcome at risk for congenital cardiac anomalies. Another objective is delineation of the course of congenital hearts from birth through 7 years in terms of specific diagnosis and condition outcome.

Methodology: a) Selection of cases with cardiovascular anomalies by computer printout of codes from periodic "summary of diagnosis" followed by detailed review of records for verifying specific diagnosis. b) Development of numerical codes of cardiac diagnosis for computer input. c) Development of a maternal data protocol coding items not available in the computer data bank. d) Using epidemiologic skills for identifying significant maternal factors impacting on pregnancy outcome.

Major Findings: 1) The study population was further identified and defined. Preliminary reports in 1965 were skewed, being weighted with the more serious cardiacs identified early by autopsy and by undifferentiated syndrome cases. The epidemiological significance of carrying the analysis thru 7 years--particularly for congenital heart disease--can be appreciated when summaries (Ped 12) indicate 931 suspect and definite cardiacs at 1 year and 412 cardiacs thereafter thru 7 years (IDC 77).

Proposed Course: The final report of this work is in abeyance pending resolution of some details and completion of another urgent project.

Publications: None

Presentations: 3

DEMYELINATING AND SCLEROSING DISORDERS

The demyelinating and sclerosing disorders sub-program includes grant support for Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), and for research directly relevant to these disorders. As of July 81 there are 93 active grants, including 6 MS, 1 ALS, and 2 ALS-MS research program project centers. Total cost expenditures in support of this research is approximately $13.837 million. A total of 104 applications were received and 72 were approved, of which approximately 8 new and 11 competing renewals were funded with a total cost expenditure of approximately $856 thousand for new research grants and approximately $2.922 million for competing renewal grants.

Multiple Sclerosis

Significant developments in fundamental research, in virology and immunology, have ocurred during recent years which have resulted in better understanding of the pathogenesis and etiology of MS.

As a consequence of Congressional interest, the Report and Recommendations of the National Commission on Multiple Sclerosis was issued in 1974. The Neurological Disorders Program of the National Institute of Neurological and Communicative Disorders and Stroke continues to implement the Commission recommendations. NDP staff recently prepared a report on the implementation of the recommendations of the National Commission on MS to the House Committee on Appropriations for Labor and Health and Human Services. Most of the recommendations have been implemented. A few of the recommendations are not capable of implementation at the present time.

As of July 81 in the Multiple Sclerosis (MS) sub-program, 35 grants were active, including 6 MS and 2 ALS-MS research program project "centers". Total costs expenditure in support of these activities is approximately $8.911 million. A total of 41 applications were received. Twelve were approved of which 4 new and 7 competing renewals were funded with a total costs expenditure of approximately $567 thousand for new research and approximately $2.617 million for competing renewal grants.

Multiple sclerosis is one of the more common chronic neurologic diseases in the United States. This disease characteristically afflicts young adults and consequently the burden on the patients and their families is multiplied in terms of societal losses.

Myelin, the protective sheath normally present around most nerve fibers is destroyed in multiple sclerosis. Characteristically this occurs in patches separated one from the other, and at unpredicatable times. There is lesser involvement of the axon itself.This process is associated with scar formation and hardening (sclerosis). The areas of demyelination, scattered in the brain and spinal cord, are often correlated with symptoms such as double vision, decreased vision, inbalance, numbness, paralysis, tremor. nystagmus, speech and elimination difficulties.

Etiology and Pathogenesis

The cause of MS is not known but recent observations have provided new and potentially significant insights into possible etiologies and pathogeneses. Epidemiologic studies indicate high and low prevalence areas for MS. Studies of migrant populations strongly suggest that MS is acquired in childhood although the clinical disease is not manifested until adult life. Epidemiologic studies suggest that the disease may be initiated by environmental agents, such as viruses. In addition, current data indicates that the frequency of HLA phenotypes is increased in the MS population compared to non-diseased controls, suggesting that susceptibility to the development of MS is determined, in part, by genetic factors. The etiology of MS is therefore probably multifactorial. Intensive efforts to isolate a causative agent from MS tissues have either been negative or not reproducible. Two recent reports identifying measles and corona viruses by application of newly developed technologies have stirred much interest but these remain to be confirmed. Much effort is currently directed towards the study of animal models infected with viruses which mimic MS. The MS program has been monitoring various reports of viral isolation and intramural scientists have sought to confirm or deny these reports by repeating these studies. These have been negative thus far.

Although the pathogenesis of MS remains undefined, there is accumulating evidence that perturbations of T cell function, particularly alterations of suppressor T cells activity, occur in MS patients.

Studies are currently underway to: 1) investigate factors which cause genetically susceptible individuals to develop MS, 2) detect changes in immunological responses in relation to clinical changes, 3) determine immunologic responses to other viruses, particularly myxoviruses, and 4) compare survival, rate of progression and disability among patients in high and low prevalence areas. Positron emission tomography (PET) has yet to be exploited but offers promise for significant insights in understanding metabolic events, and possibly vascular factors in MS.

Immunology and Virology

It is postulated that a viral agent establishes a latent infection which periodically becomes activated leading to myelin destruction. Whether this is the direct effect of the virus or a destructive immunologic reaction, possibly provoked by a secondary viral infection or a nonspecific inflammatory response is not known. The study of animal models of virus-induced demyelination is important as it allows dissection of the various facets of demyelination, i.e., morphologic, virologic, immunologic, and biochemical which are not easily studied in human material. These models are among the very few in which a combined viral-immunopathological mechanism of demyelination appears operative and therefore may have relevance to the human disease, multiple sclerosis. The relationship between viral infection and subsequent alteration of the immune system is being intensively investigated.

The possibility that MS may be due to a dysimmune state continues to be a prime consideration in the pathogenesis of the disease. The parallel drawn between animal models of experimental allergic encephalomyelitis (EAE), and most recently with relapsing EAE, which mimics MS both clinically and pathologically, has found support in recent studies which demonstrate an altered immunological status in the human disease.

One animal model of virus-induced demyelination used to investigate the morphological and immunopathological features of myelin injury is Theiler's virus encephalomyelitis.
This model is characterized by viral persistence in central nervous system (CNS) tissue and by chronic primary demyelination in the spinal cord. Immunosuppression studies demonstrate that demyelination in this model is probaby immune-mediated.

Little is known about the ability of virus to infect and produce dysfunction of the oligodendrocyte (the cell responsible for the production of myelin). Furthermore, the factors in the sera of patients with MS which can demyelinate myelinated cultures *in vitro* are not well characterized. Although some information is available regarding remyelination in MS plaques, its extent and the role of immunological or other factors which might inhibit remyelination are unknown.

The neuropathological research supported at Albert Einstein College of Medicine (AECM) has been interdisciplinary and largely directed towards the elucidation of immunopathologic events implicated in the pathogenesis of the demyelinated lesion in MS. Foremost in recent achievements has been the continued development and study of their model of chronic relapsing experimental allergic encephalomyelitis (EAE). This condition, inducible in inbred Strain 13 guinea pigs with a single inoculation of whole CNS tissue, possesses striking clinical and pathological similarities to the human MS disease. The investigators monitored the clinical, structural, and immunologic (lymphocyte population dynamics) parameters in this animal model during the relapsing course and related the findings to the situation in MS. This work reveals that these parameters fluctuate with disease activity in a manner reminiscent of MS. They also confirmed myelin basic protein (BP) successfully prevented the development of this chronic disease and that this suppression might be related to concomitant increases in certain subsets of circulating lymphocytes. Surprisingly, it was also shown that the suppression was permanent since a second challenge of suppressed EAE animals with the nervous tissue antigen failed to elicit disease. CNS repair was also enhanced in suppressed animals. On the other hand, unsuppressed guinea pigs developed new disease after a second challenge. With the initial onset of signs of EAE, it was observed that the T-cell population of circulating lymphocytes decreased significantly. By a subsequent novel experiment, they showed that this dramatic decrease in circulating T-lymphocytes was matched by the appearance of similar T cells within the CNS, suggestive of lymphocyte migration to the target organ. Of significance to the MS situation is the possibility that BP administration to chronic EAE animals prevents or alters the migration of such cells to the CNS and at the same time causes the generation of a population of cells with suppressor activity within the circulation. The application of this combined clinical, pathological, and immunological approach to chronic EAE represents one major advance in the understanding of possible pathogenetic events in MS.

Other achievements at the AECM laboratory have included: a) the production and characterization of a specific antiserum to the cell which produces and maintains central myelin, the oligodendrocyte, to be used in future immunocytochemical studies of the behavior of this cell type during demyelination; b) investigation of the possible role of an anti-oligodendrocyte antibody in the course of MS by a series of carefully controlled experiments which showed that anti-oligodendrocyte factors in the serum of MS subjects are not specific to MS, do not represent specific antibody, and do not correlate with disease activity; c) experiments using cultures of living CNS and peripheral nervous system (PNS) tissue exposed to demyelinating antiserum from animals sensitized against whole CNS and PNS tissue. This approach has been followed for many years in this laboratory in collaboration with others and permits the investigators to observe the effects of selected factors, e.g. serum, in the absence of a host immune system. Recent findings have shown that complement-depleted anti-CNS or anti-PNS serum will cause a unique proliferation of CNS or PNS myelin, respectively, in vitro. This is evidenced by the apparent stimulation of the myelinating cells to elaborate copious amounts of redundant myelin which has a unique ultrastructure. Ongoing work along these lines will attempt to characterize the serum factor(s) responsible for this unusual behavior of the myelinating cell; and finally, d) experiments to localize and characterize immunoglobulins and viral antigens within the CNS of MS subjects. While this approach provides one promising avenue by which to demonstrate the presence of specific factors in MS, these have not yet been found.

Research at the Wayne State University is focused primarily on the mechanism governing immunologic tolerance to EAE. Since self-reactive lymphocytic effector cells can be induced by appropriate immunization, it seems clear that a regulatory mechanism controls immunological self-reactivity. The immunoregulation of EAE in inbred Lewis rats has been the thrust of this group's recent research activity. They have found that suppressor cells regulate EAE and have determined the requirements for the induction of these cells.

Suppressor cells are induced by injecting rats with BP in a nonimmunogenic form i.e., without adjuvant, but EAE is not produced. The suppresor cells localize in lymph nodes and spleen and have been identified as a subpopulation of T-lymphocytes, although there is some evidence that macrophages may also function as suppressor cells. The suppressor T-lymphocytes appear to prevent the induction of disease-inducing effector cells in this model system. One implication of this finding is that the functional inactivation of suppressor cells could lead to the appearance of effector cells which in turn may cause demyelination.

It is now feasible to investigate the concept of cell differentiation and control by evaluating relevant inductive, suppressor, and expressor cell interactions in a well studied animal model of autoimmunity, such as EAE. The report that small numbers of lymphocytes readily transfer paralytic EAE makes this model attractive for the investigation of immune control of the autoimmune cell. Cell transfer of paralytic EAE by spleen cells is achieved following an obligatory step involving exposure of sensitized lymphocytes to either specific antigen or by stimulation in vitro. Observations based on this disease-transfer model has led to the postulate that the cells responsible for initiation of disease in the recipient are terminally differentiated, and as such are not controlled by any suppressor cell population. Moreover, these transferred cells do not induce suppressor activity following transfer to the recipients. The population of cells that is directly responsible for disease initiation are called EAE effector EAE(E) cells.

Since transfer of paralytic disease is now readily accomplished, it is possible to study this model of autoimmunity in the rat in terms of the disease process initiated by either active or passive disease-producing mechanisms. In addition recovery from induced EAE normally occurs in the rat so that studies of autoimmune recovery mechanisms following active or passive disease are also possible.

At present, the EAE transfer system is inadequately understood in the areas of, a) the role of the donor in providing EAE(E) cells that have the obligatory requirement of in vitro culture for acquisition of transfer effectiveness, b) the cell interactions and conditions in vitro that are required for the development of the EAE(E) population, and c) the role of the recipient in development of passive EAE in terms of recipient-cellular participation, regulatory events, and specific and nonspecific participation in the disease process itself.

A finding of considerable potential importance has resulted from the collaborative effort between Duke University Medical Center and the Northwestern University Medical and Dental School. Using their special expertise in immunochemistry and radioimmunoassay developed in the area of myelin immunology under earlier grant support, they attempted to explain why baby rats are unusally resistant to the induction of EAE. It was postulated that this display of tolerance is due to the presence of the antigen, MBP, in the circulation of these rats that dampened their immunologic response to injections of the antigens. The team at Duke University looked for immunochemical evidence that this was so in samples sent to them under code from Northwestern University. They found some samples with MBP in them and others without. When the code was broken, the MBP-positive samples were from the suckling rats and the MBP-negative ones were from adults. However, with increased sensitivity of the method, they found definite evidence of serum MBP in very low concentration in the adult also. Pursuing the analysis still further, they began accumulating indirect evidence that the serum MBP was not the intact form of the protein as it exists in the myelin sheath, but in the form of circulating fragments. Sometimes one fragment would appear and sometimes another. Infrequently all fragments were present. Currently they are isolating and purifying some of these fragments in order to have direct evidence for their existence and hopefully to pinpoint their place in the MBP molecule. The difficulties they face stem from the extremely small concentrations involved. The amount of MBP fragment in adult blood, for example, may be so small that it would take 50 gallons to yield the equivalent of a 5-grain aspirin tablet.

Thus, what began under the aegis of an NINCDS grant as an immunochemical analysis of myelin architecture some seven years ago has become an immuno-chemical search for myelin fragments in the circulation. Consequently, the assumption now is that some of the major events that determine whether "neuroautoimmune reactivity" spills over into the brain itself, take place in blood.

At the University of California at San Diego demyelination and remyelination are studied in acute and chronic toxic, autoimmune and virus induced demyelinating diseases. Different mechanisms of myelin destruction are explored by electron microscopy. Demyelination in peripheral nerves in Marek's disease follows the development of hypersensitivity to myelin after infection with Marek's disease virus. Co-cultivation of dorsal root ganglia from infected chickens revealed the presence of virus in Schwann cells. Demyelination secondary to nonspecific inflammatory reactions is studied in peripheral nerves following induction of an acute Arthus reaction by bovine serum albumin and tuberculin. The effects of antimyelin antibodies, including antimyelin basic protein and antigalactocerebrosides, are examined after injection into peripheral nerves. Virus induced demyelination followed by remyelination is explored in two experimental models in mice infected with mouse hepatitis virus and DA strain of Theiler's murine poliomyelitis virus. The former causes a selective destruction of oligodendrocytes followed by rapid remyelination. The latter induces a chronic persistent demyelinating disease with delayed and incomplete remyelination. The possibility that such persistent demyelination is caused by an autoimmune reaction is studied by demonstrating the development of hypersensitivity against myelin. Desensitization of mice to myelin basic protein or crude white matter is explored with the aim of preventing the development of autoimmune demyelination following viral infection.

The studies on peripheral nerves concerned with mechanisms leading to demyelination contribute to the understanding of the pathogenesis of human allergic neuritis, (the Guillain Barre Syndrome). In particular they are aimed at elucidating the role of antibodies against myelin vs the effect of cellular immune reactions. The studies on mice infected with either mouse hepatitis virus or Theiler's mouse poliomyelitis virus contribute to the understanding of postinfectious autoimmune demyelination believed to play a role in pathogenesis of multiple sclerosis.

The major thrust of the research at Emory University is 1) to investigate the synthesis, breakdown, and turnover of basic protein (BP) in myelin and related membranes, and 2) to investigate the possible functions of this membrane protein in myelin. A most important finding is the clear demonstration of a stable myelin in brain which is synthesized only in the young rapidly myelinating animal. This stable myelin core has been separated from the total myelin by sedimentation in a sucrose density gradient. The specific activity of the myelin proteins in this fraction does not change during the adult life of the animal. This is the first time a stable myelin fraction has been demonstrated. In the past it has only been shown that the labeled amino acids remain in the total myelin, a result which could be explained by reutilization of labeled amino acids. This explanation is not in agreement with the results of their experiments. The information obtained in studies of myelin membrane damaged by the complement system could contribute directly to the membrane modification studies. A considerable amount of work in this field with sheep erythrocyte membrane and with liposomes (artificial membranes made with known chemical components of lipid) was done. Through these experiments, we have learned that certain unsaturated lipids are more susceptible than their saturated lipid counterparts, and lipid with a longer chain length behaves like the saturated lipid when attacked by complement. Furthermore, cholesterol in the membrane protects and reduces the extent of damage.

Studies are now exploring ways of modulating the myelin lipid composition to learn what types of chemical or physical changes in the membrane can reduce myelin damage under these circumstances. It is well known that the nature of lipid in the diet can directly influence the chemical composition of cell membrane lipid. Thus, dietary lipids could influence the effector phases of demyelinating diseases. The understanding and prevention of the initiating phases of these diseases are more remote goals of these studies.

Data is being collected at Yale University on the glycosphingolipid composition of normal and pathological nervous tissues. The latter include brain tissues afflicted by multiple sclerosis and "slow viruses". Special emphasis is being placed on sialic acid containing glycosphingolipids (gangliosides), and their structures and metabolism as related to the maintenance of membrane integrity.

Understanding of the chemical architecture of myelin and the factors maintaining myelin stability is of importance. The research program at the Eunice Kennedy Shriver Center for Mental Retardation has been specifically directed to the chemical characterization of the bovine white matter proteolipid apoprotein and to the determination of its primary sequence. A major problem which must be dealt with is the tendency of the protein and the peptides derived therefrom to aggregate and precipitate. These studies are basic to an understanding of the chemical architecture of the brain and, in particular, of myelin. Proteolipid protein is quantitatively the major protein of CNS myelin. Study of its primary structure should provide a basis for understanding the unusual solubility properties of the protein, its function within the myelin membrane and its interactions with other myelin components. These studies relate to fundamental problems in membrane biology as well as to the specialized function of myelin as an insulating membrane. They should contribute to an understanding of the structural factors which maintain the integrity of the myelin sheath and the abnormalities which affect myelin stability in demyelinating diseases, including multiple sclerosis and diseases of genetic and environmental origin.

Another aspect of this study deals with the practical problem of quantitatively detecting antimyelin antibodies in the serum or cerebrospinal fluid (CSF). The only method now available involves culture of newborn mouse central nervous tissue explant. Large quantities of CSF or serum are needed in order to observe myelin destruction in this system. The culture technique is difficult and the results are not quantitative. Therefore, these investigators seek to develop assay techniques with liposomes made with extracted myelin lipid. The extent of trapped markers released from the liposomes when they are treated with antimyelin antibody and complement should reflect the titer of antibody present in the test sample.

The effect of macrophage secreted proteases on myelin degradation have been investigated as one possible mechanism of demyelination. Comparative X-ray diffraction studies of mature, immature, and abnormal myelins derived from various species are being carried out. Nuclear magnetic resonance (NMR) spectroscopy is being used to study interactions between MBP and myelin specific lipids. New techniques and instrumentation are being developed to study membrane structure and membrane models. The demyelinating effect of serum from MS patients and EAE is also being analyzed.

Scientists at the Albert Einstein College of Medicine are concentrating on cell type specific antigens of neurons, glia and Schwann cells. They have been interested in antigens such as Ran-1, a rat Schwann cell antigen, which are defined and detected only by immunological techniques, and also with markers such as filament subunit proteins, myelin glycolipids and toxin receptors which are defined by biochemical or toxin binding methods. These latter molecules can often also be visualized with specific antisera and their usefulness as markers assessed by immunofluorescence.

Laboratory Assessment

There is a real need to develop some laboratory indicator(s) to permit objective monitoring of MS activity. The Institute held three workshops, two in 1975, and one in September 1980, for the purpose of state-of-the-art assessment in the development of diagnostic tests. A number of scientists are studying the possibilities of using myelin basic protein (and its fragments) and T suppressor cells as monitoring indicators.

The recently developed oligoclonal immunoglobulin assay can confirm MS diagnosis in about 90-95 per cent of cases. However, there is great interest in developing even more sensitive and reliable diagnostic tests for MS. A highly sensitive radioimmunoassay is being used to assess demyelination and myelination using nucleotide rich material (NRM) found in the CSF which is unique to MS patients. Further, an attempt is being made to verify the presence of neuroelectric blocking factor(s) reportedly found in serum obtained from patients with MS.

A group at Johns Hopkins University and others have reported that basic protein appears in the cerebrospinal fluid (CSF) of MS patients undergoing an acute attack. The presence of myelin basic protein in the CSF of MS patients undergoing acute attacks may have practical significance in assisting in the early diagnosis of MS and permiting monitoring of the activity of the disease in patients with confirmed MS. Myelin basic protein assay in CSF may also prove to be a useful tool for measuring response to therapy.

Serum and brain tissues from MS patients and appropriate controls continue to be collected at the MS center at University of California, San Francisco. The quantitation of IgG, and IgG antibody specificity, identified from these sources, continue to be the primary activities. The laboratory is able to detect antibodies to numerous common viruses by standard and radioimmunological techniques. Specimens from the United States and Japan are analyzed. Some oligoclonal bands in the CSF of patients with MS and subacute sclerosing panencephalitis appear to contain antibodies which react with both measles virus and myelin basic protein. Because of the serological and epidemiological evidence linking measles virus to MS, evidence for persistence of the virus genome in MS tissue is sought. Very recent efforts have succeeded in identifying measles virus genome in brain tissue of two of six cases of MS, using new, highly sophisticated techniques.

Treatment

ACTH and steroids continue to be used in the treatment of exacerbations of MS. Other pilot studies are exploring immunosuppressive therapy with azathioprine, prednisone with azathioprine, and cyclophosphamide. While the steroids appear to shorten acute relapses, they do not affect progression. Some suggest that they may increase the frequency of relapses or predispose patients to earlier relapses than expected during the natural course of the illness. The alkylating agent, cyclophosphamide, appears to temporarily improve neurologic function, decrease spinal fluid immunoglobin and prevent progression. Chlorambucil appears relatively ineffective. Relapse rate and progression may be ameliorated by several years treatment with the anti-metabolite azathiaprine. Use of these drugs, moreover, is not without significant side effects. Controlled clinical trials with long term follow-up will be necessary to delineate risks and benefits. Factors that will predict response to drugs remain to be defined.

Nevertheless, because of the recent insights into the pathogenesis of M.S., it is anticipated that large numbers of proposals will be submitted to assess the efficacy of various immunomodulating agents and modalities. A preliminary study of the efficacy of co-polymer I at the Albert Einstein College of Medicine is already showing promising results.

The management of the patient's emotional status, and the effects of tension, frustation, and depression on the endocrine system continue to receive attention.

Summary

It is apparent that there is a real increase in the research effort and knowledge regarding multiple sclerosis. Although caution against over optimistic expectations of quick results is appropriate, it is increasingly evident that investment in research in MS and related disorders has resulted in attractive and promising results. Guarded optimism regarding useful intervention techniques, is appropriate.

Amytrophic Lateral Sclerosis

The human motor neuron disorders (MND), of which amyotrophic lateral sclerosis (ALS) is one, are a group of neurological disorders characterized by weakness, muscle atrophy, and widespread denervation. Some controversy exists as to whether MND's represent a spectrum of one disease or are a heterogeneous mixture of diseases with common clinical and pathological features. Genetic studies suggest a variety of modes of inheritance: autosomal recessive, dominant, and polygenic. The infantile spinal muscular atrophies are inherited as an autosomal recessive trait, and some of the familial cases of ALS appear to be inherited as an autosomal dominant. In many other families the mode of inheritance is less well defined. Most of the cases, however, are sporadic.

As of July 1981 the Amyotrophic Lateral Sclerosis (ALS) sub-program had 10 active grants which included one ALS research program project center. The total cost of these research activities is approximately $934 thousand. This includes 1 ALS "center". When the two ALS - MS "centers" are also included, the number of active grants is 12 for a total cost of approximately 2.929 million. Twenty applications were received, and 12 were approved, of which 1 new and 1 competing renewal were funded at a cost of approximately $41 thousand for the new and approximately $38 thousand for the competing renewal grant. In FY 1980 the Neurological Disorders Program issued a Program Announcement calling for grants on the Spinocerebellar and Systems Degenerations.

Etiology

The cause (or causes) of the nerve dysfunction and degeneration is not known. One theory holds that ALS is due to accelerated aging of the motor neuron, which is genetically programmed. ALS has been thought to be associated with secondary factors such as prior poliomyelitis, neoplasia, or excessive athletics. That ALS is due to multiple etiological factors is supported by the following: familial cases are either autosomal recessive or dominant; genetic and environmental interaction is seen in familial and nonfamilial clusters in Guam; and dizygotic male twins developed ALS in the sixth decade. There is some variability both in the duration of illness and in the pathology of the familial forms of the illness. Variations are also noted in the sporadic form of ALS where 20% are alive after five years. ALS has been reported in association with dementia and degeneration of other systems.

Clinical Manifestations

The clinical picture is characterized by muscle weakness, fasciculations and wasting associated with hyperreflexia. Speech and swallowing difficulties are frequently encountered. Sensory changes are not a characteristic part of this disease. It is of particular interest that cranial nerves III, IV, and VI are spared until very late in the disease. The same is true of bladder and bowel function. Urinary incontinence is a rare phenomenon and sexual function is preserved.

Epidemiology

Motoneuron disease usually occurs sporadically in the population with a prevalence which has been estimated to be 2-7/100,000 population. Although statistics are sparse and incomplete, extrapolation from a recent study suggests that about 4,000 new amyotrophic lateral sclerosis (ALS) cases are diagnosed each year. Approximately 5 percent of the patients have a family history of the illness, and in some of these an autosomal dominant pattern of inheritance is seen. Males are more affected than females, with a preponderance of 1.6-2 to 1. Several retrospective studies have shown that the mean age of onset is between 46 and 56 years. The disease is progressive and disabling. Most patients live 3 to 5 years whereas others reach a plateau and live 10 years or rarely longer.

ALS has a fairly uniform world wide distribution with some exceptions. Geographic areas of high incidence include the Kii peninsula of Japan, Guam and the Mariana Islands, and the Kepi region of New Guinea. A low prevalence has been reported in Mexico.

The histocompatatability antigens in ALS patients have been explored in a number of laboratories. HLA refers to all gene products controlled by the major histocompatability complex region which is located on human chromosome 6. Ankylosing spondylitis, psoriasis, multiple sclerosis, diabetes mellitis, and myasthenia gravis have been associated with over-representation of certain HLA determinants with respect to the general population. Numerous reports suggest an increased incidence of various other determinants in motoneuron diseases. There is an increase in A3 in ALS patients in Boston. In the Glasgow area, an increased incidence of A2 and A28 was found. An investigator in Denmark was unable to demonstrate a particular phenotype frequency pattern. Another investigator found none of these phenotype frequencies in Guamanians with ALS.

Laboratory Studies

Laboratory studies are helpful in the diagnosis of MND. Electromyography shows widespread fibrillations associated with giant polyphasic potentials and fibrillations. Motoneuron conduction velocities are typically normal. Muscle biopsy may be helpful in establishing the diagnosis. Serum and cerebrospinal fluid (CF) protein, sugar, and electrolytes are usually normal. Serum creatinine phosphokinase (CPK) as well as other muscle enzymes may be somewhat increased in about half of the patients.

Treatment

At present, there is no effective treatment for ALS. Symptomatic relief of excessive salivation may be achieved pharmacologically. Past treatments which have proven ineffective include neurotoxin, corticosteroids, immunosuppression, immunostimulation, transfer factor, and plasmapheresis.

Pathology

Examination of the central nervous system (CNS) discloses selective degeneration and loss of the large motoneurons of the ventral horns of the spinal cord and brain stem nuclei. The nuclei of cranial nerves III, IV, and VI and of the medial sacral (S2) motoneurons in the spinal cord are characteristically spared. These findings correlate with the clinical signs. There is secondary degeneration and gliosis of the corticospinal tracts. The posterior columns are spared except in familial cases. In ALS the earliest axonal loss occurs in the long peripheral nerves and corticospinal tracts, initially in the zone most remote from the cell body. This pattern of "dying-back" degeneration is probably a reflection of failure of the cell machinery to provide for its most distal parts. Another observation, emphasized recently, is the presence of swellings of the proximal portion of the axons, early in the disease. The swellings, containing large numbers of neurofilaments, are quite commonly identified in the anterior grey matter in classic sporadic ALS and in familial cases, as well as in Werdnig-Hoffmann's disease, a motoneuron disease of early life. The swellings disappear as the motoneurons die, and are rarely seen in end-stage disease when the majority of motoneurons have disappeared. It has been suggested that these swellings are the result of some abnormality in the dynamics of transport of axonal materials. The axoplasmic transport system is important in maintaining the functional integrity of the nerves and the reciprocal interdependence between them and the target cells. Other pathological changes which have been described are a variety of "inclusions" and "bodies" within the cytoplasm of neurons from classical and Guamanian ALS cases. Some of these are due to neurofibrillary alterations taking the form of ring-like or herringbone arrangements. Similar changes are found in brains of patients in their 70's and 80's. Some of the Guamanian patients showed these changes as early as 28 years of age.

Heavy Metal Intoxication

The etiology and pathogenesis of MND are unknown. Heavy metal intoxication is one of the more popular suggestions. Lead intoxication may result in a motor neuropathy in the absence of any sensory signs. Organic mercurial compounds have been reported to cause MND in patients poisoned by a fungicide used on wheat. A more recent retrospective study has suggested that a history of exposure to mercury and lead is more commonly elicited in ALS patients than in controls. CSF lead levels have been reported to be higher in ALS patients than in subjects with other neurological diseases (OND) and normal controls, whereas plasma lead levels show a lesser change. It is proposed that the normally efficient "trapping" mechanism performed by the erythroid series in the bone marrow is defective in ALS patients. Another suggestion is that lead is more avidly taken up by ALS than by normal nerves, and transported by retrograde axonal flow, causing neuronal cell body damage. Not all investigators report elevated lead levels, and further analyses are required.

Aluminum has also been implicated. High concentrations of aluminum have been found in certain neurologic conditions such as Alzheimer's disease, progressive encephalopathies associated with industrial exposure, and in uremic patients undergoing hemodialysis. In addition, aluminum experimentally leads to neurofilament concentration in neurons and possibly impairment of axonal transport. This may be important since enhanced aluminum absorption from the intestine occurs with parathyroid hormone administration, and hyperparathyroidism may be associated with MND.

Selenium toxicity has also been suggested. A preliminary report indicates that during a ten-year period, four cases of ALS had been found in a sparsely populated county (population 4,000) in west central South Dakota. In this region naturally occurring selenium intoxication had been endemic in farm animals. This study has been challenged as not statistically significant.

Metabolic Considerations

It is well known that neurogenic atrophy may be encountered in some metabolic disorders, such as hyperadrenalism. In ALS patients, however, defects of carbohydrate metabolism have been noted on several occasions in ALS patients. Abnormal glucose tolerance, tolbutamide tolerance and subnormal insulin secretion have also been found. Impairment of pancreatic exocrine function has also been reported with decreased neutral fat uptake, mild steatorrhea, and an abnormal response to secretin stimulation. These results are controversial and additional studies are needed.

As mentioned, neuromuscular dysfunction has been associated with hyperparathyroidism. The recent description of neurogenic atrophy associated with parathyroid adenomas and increased parathyroid hormone (PTH) deserves closer scrutiny. This is of interest since a very occasional ALS patient has been found to have frank hyperparathyroidism and many patients with hyperparathyroidism have a MND-like abnormality. This is particularly important since PTH may increase the absorption of aluminum from the gastrointestinal tract. The association of these various toxic and metabolic disorders with a motoneuron-like disease is of great interest. Thus far, however, none of these factors has been found to be definitely operative in classical ALS.

An investigator at the University of Maryland is studying the mechanism whereby muscle glucose 6-phosphate dehydrogenase (G6PD) is neurally regulated. G6PD is the rate limiting enzyme in the pentose phosphate pathway and is increased in otherwise normal neurons after denervation or application of myotoxic drugs. It had been suggested that the rate of increase of this enzyme is related to nerve stump length. This was recently confirmed, although interrupting axonal transport with vinblastine impregnated silastic cuffs did not cause an increase of this enzyme. A series of studies is now proposed to look further at the relationship of neural influences on G6PD.

Anterior horn neurons have a particularly high level of G6PD and hence might have a greater capacity for hexose monophosphate shunt activity than other nerve cells. In ALS, G6PD was found to be normal. Some investigators have found that anterior horn cells had a relatively higher level of energy utilization than other spinal cord neurons. Alpha motoneurons also appear to be richer in phosphorylase and in lysosomal enzymes than other neurons.

The normal G6PD level in ALS is of interest because of the findings of a three-fold increase of G6PD in neurones following axonal injury and during chromatolysis. The normal G6PD levels in ALS may indicate either that ALS neurons cannot respond to axonal injury, or that the axonal injury is not primary. A decrease in the oxidative enzymes, acetyl cholinesterase, thiamine pyrophosphate, and cyclic AMP and an increase in acid phosphatase were found in the CNS of some ALS patients. A histochemical study of MND showed a decrease in two membrane enzymes, ATPase and 5-nucleotidase. This study also showed abnormalities in the nucleus, suggesting a progressive inhibition of DNA-directed messenger RNA synthesis. Some quantitative biochemical analyses on the spinal cord from a Guamanian ALS patient disclosed normal levels of malic and lactic dehydrogenase, hexokinase, glutamic acid dehydrogenase, G6PD, and hydrolytic lysosomal enzymes.

Of interest is the recent identification of an ALS-like syndrome in a 24 year-old with hexosaminidase deficiency, by a group at Columbia. One young adult with a similar deficiency and clinical picture had been identified earlier.

Suggestive abnormalities in the biochemistry of putative neurotransmitters have also been described. The spinal fluid of some ALS patients has been shown to contain low levels of homovanillic acid (HVA). This was attributed to reduced dopamine synthesis in the CNS since the probenecid-induced accumulation of HVA was also reduced. Following L-Dopa therapy, there was a marked rise in HVA, but no clinical benefit was observed.

Cyclic AMP has also been found to be low in the spinal fluid (CSF) of some ALS patients as well as in patients with other diseases such as spinocerebellar ataxia. Administration of a phosphodiesterase inhibitor to ALS patients resulted in significant elevation of CSF cyclic AMP levels. However, there was no clinical change. ALS patients do not have a low level of CSF cyclic GMP or low serum levels of cyclic AMP or GMP. The low levels of cyclic AMP in the CSF could be due to neuronal death or could reflect an absence of a specific neurotransmitter. The most recent biochemical studies identified abnormal levels of free amino acids, such as tyrosine and basic and aromatic amino acids in 12 ALS patients. These patients also had statistically significant elevations in CSF total basic amino acids including leucine. These findings are suggestive of defective membrane transport in the CNS.

Any observation indicating abnormalities in brain tissue that are not explainable by loss of motoneurons offer important clues for further investigation. At St. Vincent's Hospital in New York, ALS and control brain specimens were studied for the distribution of gangliosides. Gangliosides are lipid materials present in membranes of neurons which act as receptors for various toxins, e.g., cholera toxin. An abnormal distribution of gangliosides was found in the pre-motor cortex of ALS patients. The average distribution of four major ganglioside species in eight ALS brains was abnormal. Advanced instrumentation allowing measurement of up to ten ganglioside species permitted obtaining data which suggests a metabolic defect in ALS at the step in which a one-ganglioside species is formed. This in turn suggests a deficiency in transferases which are required for such conversions. These data need to be confirmed.

Neurotransmitters and Receptors

Neurons relate to other elements by establishing neuronal-neuronal, neuronal-glial, and neuronal-muscle interrelationships. It is postulated that these cellular relationships are important in the synthesis and release of neurotransmitters, the expression and maintenance of receptors, and the generation of trophic factors necessary for the health of the motor unit. In addition to direct connections from the large pyramidal neurons in the motor cortex, the alpha motoneurons in the anterior horns of the spinal cord receive input from group 1a muscle spindle afferents, and from the tracts descending from the vestibular nuclei, brainstem reticular formation, and the red nucleus. The major synaptic input, however, is from the poorly defined spinal cord interneurons. The putative neurotransmitters in the spinal cord have not as yet been defined. Anterior horn cells have receptors for gamma-aminobutyric acid (GABA) and there is good evidence for postsynaptic activity of glycine, alpha-alanine, beta-alanine, taurine, aspartic acid, and glutamic acid. Many studies remain to be done on neurotransmitters in ALS patients, particularly in regard to their synthesis and release, and the state of their receptors.

Extensive investigations of function at the synaptic membrane have not been done. Reactive changes such as axonal sprouting occur in ALS. Axonal sprouting can be the result of inhibition of transmitter release at the presynaptic membrane. Such is the case with botulinum and tetanus toxins, where, following denervation, regeneration occurs in the form of axonal sprouting from intact nerve terminals.

Trophic factors which influence the expression of receptors, the release of transmitters, and the general maintenance of neuronal health, have been studied largely in the developing nervous system. However, in recent years, the mature nervous system has received attention. Experimentally induced changes in the peripheral nervous system, such as physical and biochemical axotomy and interference with neuromuscular transmission, and muscle destruction, cause biochemical and morphological abnormalities in both developing and mature ventral horn cells. Axotomy also causes changes in the shape of excitatory postsynaptic potentials of motoneurons as well as failure of Group 1a synaptic connections. Axotomy has also been found to cause loss of muscarinic receptors and loss of synaptic contacts in the hypoglossal nucleus suggesting that the presence of receptors is necessary for the maintenance of the physical contact between pre- and postsynaptic elements by acting as a trophic influence.

The feedback interplay between muscle and neuron has yet to be defined. Some basic work has suggested that the contractile and metabolic characteristics of muscle fibers are tightly coupled with the biochemistry of motoneurons. Fast and slow muscle biochemistry is determined by the motoneuron. Rat motoneurons exhibit changes in the G6PD and acid phosphatase following repeated contraction, and chromatolysis occurs in motoneurons of mice exhausted by swimming. Finally, it was found that the activity of choline acetyltransferase, the enzyme involved in the synthesis of acetylcholine, was significantly greater in combined cultures of spinal cord and muscle cells than in cultures of spinal cord cells alone. The increased activity of this neuronal enzyme is associated with the formation of functional neuromuscular junctions in culture.

The failure of transmitter release, receptor sensitivity, and trophic influences may all depend on intact axonal function. As described previously, the two suggestive findings implicating impaired axonal function in ALS are the presence of filament-rich proximal axonal swellings and the severe degeneration in the lumbosacral levels of the corticospinal tracts, and distally in the peripheral motor nerves implicating a "dying back" process. Interestingly, Dapsone (4, 4-diaminodiphenylsulfone), a drug used in skin diseases and leprosy, produces an axonal disease of motor nerves in humans, characterized by the "dying back" phenomenon. Recovery from drug related damage occurs by regeneration of axons and by peripheral sprouting of non-damaged axons.

Virology and Immunology

Attempts to transmit MND to chimpanzees (Gibbs and Gadjusek) by innoculation of brain and spinal cord tissue from patients with ALS have so far been negative. Despite the expectation of uncovering a latent or persistent virus infection in ALS, the search for the presence of virus has been unrewarding. There are only vague suggestions of immune dysfunction in ALS, which require additional study.

There are a number of reasons to implicate viruses in the etiology and pathogenesis of motoneuron disease. These include the following: 1) There are other known noninflammatory, progressive degenerative central nervous system diseases due to viral-like agents. These are progressive multifocal leukoencephalopathy, Cruetzfeldt-Jakob disease and kuru. 2) ALS patients give a history of antecedent paralytic poliomyelitis at rates up to ten times that of control patients. Few patients, following paralytic poliomyelitis, develop a slowly progressive, although for the most part benign, motoneuron disease. 3) Recent studies of tissues from ALS patients suggest that there is a defect in a DNA directed messenger RNA. A variety of viruses are known to interfere with host cell micromolecular synthesis. These include picorna viruses such as polio, pox, and some paramyxoviruses such as Newcastle disease virus. 4) A transmissible C-type virus has been found to cause a type of motoneuron disease in the aging population of a wild mouse colony. 5) RNA-directed DNA (a reverse transcriptase), an enzyme associated with oncoviruses, has been demonstrated in the brain of Guamanian ALS patients and normal controls, but not in American AL~ patients. 6) Picorna (polio, coxsackie, and ECHO) virus-like crystals have been seen in muscles of a single patient with ALS.

Numerous attempts to isolate virus from ALS tissues have failed. Virus isolation from the tissues is a very difficult task, especially from human central nervous system tissues. The possibility of a latent or defective virus makes isolation impossible because the complete viral genome may not be present.

Viral infection of neuroblastoma cultures has been achieved with a number of viruses including rabies virus, the JHM strain of mouse hepatitis virus, herpes virus and others. It has recently been shown that the virulence of rabies virus could be increased by serial passage in neuroblastoma cells, but not in cells of non-neural origin. Thus, neuroblastoma cells may serve as a more appropriate host for the study of neural infection than non-neural cells. Conversely, virus can have an affect on neuronal differentiation and function.

The most striking findings in ALS are pathological changes in the motor neuron. Therefore, it is reasonable to focus on viruses that selectively infect the neuron, especially motoneurons. An investigator at the University of Southern California has chosen to study mouse polio virus "Theiler's virus" because it produces both an acute and an indolent neuronal infection. It is also advantageous to study this virus as it grows both in mice and in cultured cells of murine origin such as neuroblastoma.

ALS and ALS-Parkinson's dementia syndromes which occur in Guam have been investigated for slow virus activity. However, experiments supporting the transmission of ALS to Rhesus monkeys have not been reproduced, and the isolation of an ALS agent has not been accomplished.

The lack of serological evidence does not rule out a viral infection. It is becoming increasingly clear that chronic progressive viral CNS disease may not be accompanied by a serum or CSF antibody response to the causative agent. A wide variety of immunologic indicators of disease have been studied. Neutralizing antibodies to polio, mumps, herpes, and influenza viruses were similar in ALS patients and controls. Guamanians with ALS have similar levels of antibodies to herpes, cytomegalo, and Epstein-Barr viruses as compared to age and sex-matched controls. The immunoglobulin levels in twenty-one patients were found to be normal. Five of thirteen patients in this study with progressive multifocal encephalopathy showing no evidence of pyramidal tract involvement, did have elevated levels of serum IgM. The percent serum immunoglobulin in sixteen motoneuron disease patients was higher than in eight controls, but not higher than in six patients with other neurologic diseases.

Immune complexes measured by the CIQ assay were demonstrated in the sera of ten of twenty-five ALS patients. In that study, renal glomeruli from nine of thirty-three ALS cases showed no IgG and C3. The deposited complexes, after elution, showed no immunologic reactivity to poliovirus. A similar study was done on sera from patients with ALS and Parkinsonism-Dementia (PD) on Guam. Three of five ALS patients and four of twelve PD patients showed significant binding of CIQ. Circulating immune complexes were also reported in ten percent of ALS patients using the Raji cell method for detecting immune complexes. There is, therefore, a suggestion that immune complexes are present in the sera of ALS patients but the nature of the antigenic component has not been defined.

Skin tests for delayed hypersensitivity are normal. It is stated that a generalized anti-inflammatory response had been noted in some ALS patients. Skin testing of Guamanians with ALS and PD to recall antigens showed diminished responsiveness. A lessened response has also been found in patients with bulbar ALS. In contrast to these studies, a whole host of immunologic studies in ALS patients for a variety of antigens such as basic protein, crude brain extract, and purified acetylcholine receptor have been negative. T and B cells have also been found to be normal. Total lymphocytes were reported to be elevated in ALS as compared to controls but not when compared to other neurologic diseases.

A "cytotoxic factor" in sera of ALS patients has been detected by in vitro tests using mouse neonatal brain. Whether or not this factor is active in vivo is unknown. This study is complicated further since it has been observed that cytotoxic activity can occur in the sera of patients with other neurological diseases. Serum factors have also damaged anterior horn cells in vitro. In a follow-up study it was recently found that sera from six of twelve ALS patients, one of three normal controls, three Duchenne muscular dystrophy patients and one of two spinal muscular atrophy patients, were positive. These studies could not be repeated. The factor in human sera which appears to be toxic to rodent anterior horn cells has not been identified.

At the "ALS - MS Center" at the Scripps Clinic and Research Foundation, several approaches are taken to achieve a better understanding of neurological and immunological mechanisms in neurological diseases with the aim of uncovering the etiology and/or pathogenesis of multiple sclerosis, amyotrophic lateral sclerosis and other "degenerative" diseases of the nervous system. These studies include work on viral persistence, immune modulation of viral antigens on the cell surface, killer and suppressor cells in experimental models and in man, and effects of persistent virus infection on differentiated cell functions. The studies employ a wide spectrum of modern immunological technology, some of which has been developed by these investigators.

At the "MS Center" at St. Vincent's Hospital in New York in the past year, a search for Actinomycin-D resistant RNA was successful in 2 ALS cases. Search for adeno-associated virus (AAV) was negative in 8 ALS cases although antibodies to AAV are increased.

Animal Models

Animal models of MND are of particular importance to allow manipulations which cannot be used in human patients. An animal model of motoneuron disease should meet the following criteria: 1) motoneurons should be selectively affected; 2) the time course of the disease should be readily predictable; 3) the disease should be reproducible in laboratory animals; and 4) the pathology should share features in common with the human disorders. Several animal models have been described but unfortunately, most of them do not resemble human motoneuron disease.

The best model now available is hereditary canine spinal muscular atrophy. Other models include Wobbler mouse, Swedish Lapland dogs, Stockard's paralysis in large dogs, and murine retrovirus poliomyelopathy. Toxic models are also being investigated.

Breeding studies at Johns Hopkins have been successful in producing hereditary canine spinal muscular atrophy in Brittany Spaniels. The disease affects both sexes. Based on their initial findings, the disease appeared to be inherited as a dominant trait. The phenotypic expression of the disease varies with the age of onset, progression of the disease, and pathological changes. Three types (I, II, and III) have been recognized: accelerated, intermediate, and late onset chronic disease. The neuropathology correlates well with the clinical manifestations of disease. Pups with Type I form of disease have massive numbers of swellings in the proximal axons, as well as neuronophagia, chromatolysis, and glial bundles in the anterior horns. The latter three features are considered to be characteristic of Werdnig-Hoffman disease. The intermediate form of the disease has a marked loss of motoneurons with concomitant decrease in the number of axonal swellings. Within the ventral horns, there are empty baskets which once contained motoneurons. In the ventral roots are glial bundles similar to those in pups with the accelerated type of the disease. It has been suggested that protective genes are operative in Types II and III. Corticospinal tract degeneration has not been identified, as yet, in these dogs.

The Wobbler mouse, an inbred strain, develops paralysis during the first week or or months of months of life. The disease is not confined to motoneurons and affected cells show changes unlike the abnormalities seen in the human motoneuron diseases.

In Swedish Lapland dog models, the illness begins suddenly in puppies. Motor functions are impaired over about two weeks, and subsequently there is little progression of disease. Neuropathologic abnormalities are widespread and the disease is not considered a selective abnormality of motoneurons.

Dogs with Stockard's paralysis have never been studied extensively. Unfortunately, breeding stock is not available at this time.

Transmission experiments in the murine retrovirus poliomyelopathy model, indicates that the paralytic disease is due to infection with neurotrophic retrovirus (type cRNA virus). Affected animals develop progressive paralysis over days to weeks. Neuropathologic changes occur predominantly in the lumbosacral spinal cord with both the gray and white matter being affected. The disorder is under active study in the neurovirology laboratory at the Johns Hopkins Medical School.

Recently, a mutant strain of Syrian hamster, showing hind leg paralysis discovered at Montefiore Hospital and Medical Center, was utilized in a study to assess its correspondence to certain human neuropathies, specifically ALS. The study has centered on the electron microscopic changes of peripheral axons and their coverings, the myelin sheaths. Changes in Schwann cells, accumulation of Hirano bodies, and associated filamentous accumulations and swellings in neurons were observed. These studies are done on both young and old hamster mutants. The results confirm earlier findings that the Schwann cell membrane disappears at the region of filament accumulation and onion bulb formation. These studies are being continued in an effort to understand the relationship of the morphological changes to each other and to the symptoms they produce.

Toxic axonopathies, of which B,B imidodiproprionitrile (IDPN) model is one, are produced by an extensive and diverse list of environmental and pharmaceutical agents. The public health implications of toxic axonopathies have been increasingly apparent in recent years. Beyond the clinical importance and the implications for public policy, several toxic neuropathies offer potentially important probes for investigations of the pathogenesis of neurologic disorders and, in some instances, of basic neurobiological phenomena. Experimental toxic neuropathies are particularly accessible to detailed pathological and biochemical study with defined variables. For the most part, they faithfully reproduce the human pathology and provide opportunities for experimental manipulation, axonal transport studies, and quantitative neuropathological approaches.

In experimental intoxication by (IDPN), in hereditary canine spinal muscular atrophy, and in MND, chromatolysis (a reaction to axonal injury) is a rare finding. These observations have supported the hypothesis, suggested earlier, that neuronal death in MND is secondary to the inability of motoneurons to respond to axonal damage. Again it is not known whether the failure to observe the classical changes of chromatolysis in most cases of MND is due to the failure of the "signal" from the periphery to arrive, due to the inherent failure of the motoneuron to receive and translate the "signal", or may merely indicate that the primary defect is in the cell body.

Investigations at Johns Hopkins University attempt to understand the ways in which neurons are affected by or respond to disease processes, including traumatic injury, genetic factors, and toxins. The strategy has been to study animal models of human disease using a variety of approaches derived from contemporary neurobiology. They have used IDPN in dogs and cats to induce axonal swellings. The initial short-term studies reveal striking clinical differences between dogs intoxicated with IDPN and rats similarly treated. They have succeeded in producing chronic disease in dogs by giving IDPN for long periods (9 months or more). It was thought that the large animal model would allow studies that were particularly difficult or impossible to perform in the smaller rat model. Utilizing radio-labeled proteins, they are determining the rates of slow anterograde transport. These studies have proved more difficult in dogs than in rodents. The large musculoskeletal system of dogs virtually precludes rapid removal of fresh tissues without severe disruption of other tissues needed for ultrastructural studies. Radiometric studies in the chronically intoxicated dogs show an accumulation of radioactivity in the ventral roots. The retained radioactivity parallels the distribution of axonal swellings. It appears from studies in rats that defective slow axonal transport of neurofilament proteins underlies the axonal pathology.

They have also initiated studies of the neurotoxic effect of two of the commonly used antineoplastic drugs; misonidazole and cis-platinum, which may represent new models of peripheral neuropathy.

An investigator at Mount Sinai conducts experiments to determine the biochemical changes occuring in distal axonal neuropathy caused by acrylamide and methyl butyl ketone. Emphasis is place on possible changes in lipid metabolism and axonal transport. The effect of these agents on the synthesis of lipids in lymphocyte membranes is also being evaluated. The information obtained from this study may be useful in screening agents for toxicity.

Ectropic wild mouse type C virus-induced paralytic disease in mice is similar to several "slow virus" diseases in animals and man including human motoneuron diseases and spongiform encephalopathies. An investigator at the University of Southern California is studying the mechanism of replication and determination of viral gene expression at the transcriptional and translational levels in neurons of paralyzed mice. The investigation focuses on the interaction of subvirion components with mouse neurons, which may alter or damage the neuronal membrane with consequent development of paralytic disease. These studies on virus replication and gene expression in the central nervous system of paralyzed mice will provide insight into possible mechanism of neurodegeneration in parallel diseases of animals and man. These studies of in vivo passage and virus replication suggest that infection in the neonatal period may be an important step in induction of paralysis. The results also indicate that genetic recombination of replicating virus is not an essential step in the development of neurodegenerative paralytic disease.

Conclusions

Motor neuron diseases constitute a host of disorders concerning which little is known. The most productive research related to ALS is peripheral to it, and its significance to the human disorders is moot. New ideas and initiatives are needed which will, hopefully, lead to an understanding of these disorders and thus to effective management and/or prevention.

Ataxia

As of July 1981, the Ataxia subprogram had 4 active grants. The total for these research activities is approximately $222 thousand. In FY 1981 five aplications were received and two were approved and funded at a cost of approximately $121 thousand. In the FY 1980, the Neurological Disorders Progam issued a Program Announcement calling for grants on the Spinocerebellar and Systems Degenerations.

The ataxias include a variety of disorders, primarily heredofamilial, currently classified on the basis of clinical and pathological features. Although ataxia may be a part of the clinical picture of a whole host of disorders, the primary interest of this subprogram is in those in which uncoordinated movement, due to involvement of the cerebellum and/or its pathways, is a principle feature. Other tracts and nuclei are also affected in some of the ataxias.

Estimates of people afflicted with ataxia range from 5,000 up to 20,000, in the United States. The symptoms of ataxia may begin during childhood, adolescence, young or mid-adulthood, depending upon the disorder. The causes of cerebellar ataxia include developmental defects, such as cerebellar agenesis and hypoplasia, progressive degenerative disorders, such as familial spino-cerebellar degeneration, Friedreich's ataxia, and ataxia telangiectasia. Other causes are trauma, CNS infection or its sequelae, cerebellar tumors, and environmental toxins.

In addition to faulty muscle coordination, speech impairment, lateral curvature of the spinal column, deformity of the feet, and muscle weakness, especially of the lower extremities, may be seen. The sensory and visual systems and higher cerebral function may also be affected.

Friedreich's ataxia is one of the most common forms of ataxia. It is a heredofamilial disease, but sporadic cases are not uncommon. The onset is usually in the first or second decades of life. In many cases, it is slowly but steadily progressive. Rapid progression or abortive disease is also encountered. Up to 20% of Friedreich's patients have evidence of diabetes mellitus. Many more show evidence of cardiac involvement. No specific treatment is known.

Scientists are inquiring why some families with Friedreich's ataxia have disorders of pyruvate metabolism, which is due to defects of the pyruvate dehydrogenase multi-enzyme complex, or to one or another of its component enzymes, especially lipoamide dehydrogenase (LAD). The long term goals of research in this area are: a) to test the hypothesis that there is a structural alteration of LAD in patients belonging to certain families with Friedreich's, and b) to clarify how these alterations, demonstrated in peripheral tissues, reflect changes of the enzyme in the central nervous system. The ataxia unit at the University of California at Los Angeles has been engaged in research in characterization of the biochemical defects, their possible use as diagnostic tools, and whether or not this information may be helpful in the development of treatment for inherited ataxias of various kinds. In this research, the primary focus has been on a drug called physostigmine, one of the first drugs reported to modify ataxia in man. The majority of patients had less ataxia when treated with physostigmine than with placebo. A great deal of work remains to be done to determine the validity of these results.

Despite this new information, no specific biochemical defect has been found in the majority of the patients with clinically and pathologically defined hereditary ataxias. These include the cerebello-olivary ataxias, olivo-ponto-cerebellar atrophies (OPCA), spastic ataxia, and the patients with Friedreich's ataxia without pyruvate dehydrogenase deficiency. However, recent post mortem studies of patients with dominantly inherited olivo-ponto-cerebellar atrophies (OPCA) show alterations in aspartate and taurine levels in the cerebellum, which may be the result of degeneration of olivo-ponto-cerebellar fibers. Other studies have uncovered abnormalities in brain and fibroblast proteins, as shown by two-dimensional gel electrophoresis, in patients with a dominantly inherited spinocerebellar syndrome having similarities with OPCA. The significance of this observation has not been established. Consequently, a group at Mount Sinai School of Medicine, which showed a significant decrease in glutamic acid dehydrogenase (GDH) activity in leukocytes and fibroblasts of patients with OPCS, is attempting to find answers to the question whether the enzymatic defect is causally related to the clinical syndrome, or merely an associated phenomenon.

Studies at the University of Mississippi have shown that spino-cerebellar ataxia segregates in a large kindred, and is distributed in an autosomal dominant inheritance pattern. Their preliminary results have shown linkage with the HLA histocompatability complex. Since crossing over between the spinal cerebellar ataxia gene locus and the HLA region will occur at a rate of about 13 percent, they are assessing the possibility that glyoxalase I and pepsinogen 5 may serve as additional markers. The linkage to glyoxalase will require additional investigation, since this is a much less informative locus in terms of the number of testable alleles, and only a tenuous linkage has been demonstrated. Additional information is needed both from the large kindred they have previously studied and from additional families currently under investigation. These linkage relationships are readily testable, and should provide important information for human gene mapping, as well as for the direct application of the linkage data to genetic counseling in these families. Most of the inherited ataxia research in the past has consisted of correlating clinical and pathological changes and classifying these somewhat arbitrarily as syndromes. About 60 categories have been described. Each has been considered an untreatable disease of unknown cause.

A promising new animal model, canine inherited ataxia in the Gordon setter dog, has been identified by scientists at The Johns Hopkins University. There are significant clinical and histological similarities, as well as some pathological differences, between the animal and human ataxias. Clinical, morphological and genetic studies, currently in progress, will hopefully demonstrate the significance of this potentially valuable animal model.

The immediate questions for future research that arise from present body of knowledge, as far as ataxias are concerned, may be the following: the relation between pyruvate flux and enzyme activities in specific types of brain cells; the relation between pyruvate flux and defects of other oxidative enzymes associated with ataxia; the relationship between pyruvate flux, axoplasmic flow, membrane synthesis and repair, and so-called trophic functions; the contribution each transmitter makes to cerebellar function; the anatomical and pharmacological sites of action of cholinergic agents in human and inherited ataxias; the degree of correlation between cholinergic effects and the underlying biochemical defects in man; the mechanism by which cholinergic drugs improve the signs and symptoms of ataxia; and, to what extent typical viruses or latent viruses contribute to the inherited ataxias.

INFECTIOUS DISEASES OF THE NERVOUS SYSTEM

The Infectious Diseases subprogram supports investigations of viral, bacterial, and parasitic infections, of the nervous system and any infectious agent that might be suspected to be the cause of degenerative brain diseases.

As of July 1981, 35 grants were active in the infectious diseases subprogram. This includes one program project center. Total costs for these research activities is approximately $3.253 million. A total of 35 applications were received. Thirty-one were approved, of which 5 new and 5 competing renewals were funded at a total cost of approximately $806 thousand for new research grants and approximately $272 thousand for competing renewal grants.

The aims of this subproject are: 1) to determine the etiology of subacute progressive degenerative diseases of the central nervous system of man by experimental transmission of these diseases to animals; 2) to develop workable, efficient and economical animal models for characterization of the isolated etiological agents of these diseases; 3) to uncover chemotherapeutic regimens for the prevention and/or control of these diseases in animals and to determine their safety and efficacy for use in man: 4) to study viral, bacterial and parasitic diseases of the nervous system.

General Background

It is suspected that some diseases or disorders are caused or induced by viruses although a particular virus has not been identified. These include: Reye's syndrome, Guillain-Barre syndrome, multiple sclerosis, amyotrophic lateral sclerosis, and various others such as some forms of Parkinson's disease, congenital defects, rheumatoid arthritis, and leukemia.

A permissive cell infected by virus is a cell which allows viral replication which results in the production of complete, infectious, viral progeny virions. Variations of productive virus-cell interaction allow many different viruses to establish a persistent infection associated with the continuous release of virus. In contrast, some cells are nonpermissive for viral replication, and although the cells are infected, the infection is abortive in the sense that it does not lead to the production of infectious progeny. There are many instances of abortive infections in which the process of viral replication can be arrested at any step following entry of the viral genome into the cell. Although viral constituents are synthesized, either no viral particles or only noninfectious particles are produced. This kind of abortive infection may have a profound effect on cellular metabolism and division. In many cases, abortive infection does not lead to death of the cell. The importance of abortive infections lies in the models they provide for study of viral latency: e.g. herpes viruses, and those diseases in which viral etiology is suspected but infectious virus cannot be readily isolated.

A special and interesting class of aborted infections is due to genetically defective viruses which can produce infectious progeny in cells infected at the same time by a helper virus which provides a missing constituent. After an acute infection has disappeared, a latent infection may persist, small amounts of virus may be produced, and an immune response may or may not be present. In a latent infection incomplete or defective virus might be produced in small numbers, overt disease does not occur, and the virus is not eradicated.

The infection of permissive cells with lytic viruses usually leads to active infection and cell death. However, many animal viruses which are considered to be highly cytocidal can establish infections of cell cultures that result in long-term multiplication of the virus at the same time that the cell continues to grow and divide.

The following virus-host cell relationships may be established in persisitent infections: persistent noncytocidal infections transmitted through cell division, persistent non-cytocidal infections transmitted by release of virus and infection of new cells, and persistent non-cytocidal infections involving cells which are semi-permissive or non-permissive for the infecting virus.

Slow infection of the nervous system can be caused by both conventional viruses and unconventional agents: The unconventional agents are unique: Their structure and composition have not been defined, they have not been demonstrated to be immunogenic, they have never been convincingly visualized by electronmicroscopy, they cause widespread infection with long incubation periods, and the clinical disease and pathological changes are limited to the CNS. The pathology is noninflammatory and consists of a degenerative process characterized by vacuolization of neurons and astrocytes, neuronal loss, and gliosis.

Naturally occurring slow virus infections caused by unconventional agents in man are: Kuru and transmissible dementia of the Creutzfeldt-Jakob type which can be sporadic or familial. Slow infections of man caused by conventional viruses are: subacute post-measles leucoencephalitis caused by paramyxovirus, a defective measles virus; subacute sclerosing panencephalitis (SSPE) caused by paramyxovirus, also a defective measles virus; subacute encephalitis caused by Herpes simplex virus and adenovirus, specifically types 7 and 32; progressive congenital rubella caused by rubella virus; progressive panencephalitis as a late sequella following congenital rubella by Togavirus, a defective rubella virus; and progressive multifocal leuoencephalopathy (PML) caused by papovavirus. There are numerous other slow infections known to be caused by conventional viruses such as picornaviruses (poliomyelitis, echovirus), parvoviruses, and others. Some of these, such as visna in sheep, canine distemper in dogs, and Theiler's virus in mice are possible models of human disease.

Following the development in recent years of the concept of "slow" and "latent" virus infections and the discovery that Kuru and Creutzfeldt-Jakob disease are caused by transmissible agents, there has been a flurry of activity in the search for the possible viral etiology of multiple sclerosis and other "degenerative" CNS disorders. Viruses of the herpes group have been found to be "latent" in nervous and other tissues of asymptomatic individuals. The varicella-zoster virus may be "latent" in dorsal root ganglia of the spinal cord and its reactivation leads to clinical herpes zoster. Human cytomegalovirus may remain latent and be activated by immunosuppression in renal transplant patients. Epstein-Barr (EB) herpesvirus may be "latent" in lymphocytes of individuals who have had infectious mononucleosis. Latent infectious herpes simplex virus (HSV) has been isolated from the trigeminal and dorsal root ganglia of humans and experimental animals. In one study "latent" HSV infection of the trigeminal ganglion was found in 50 per cent of unselected individuals at autopsy.

The identification of viroids by plant pathologists during the past 20 years may help direct the search for unconventional agents. Viroids are fragments of RNA or DNA which lack a protective protein coat and can therefore be inactivated by RNAase or DNAase. Viroids consisting of RNA have been identified in about a dozen diseases of plants which are characterized by stunted growth. A DNA viroid is strongly suspected as the cause of a repeated epidemic of lymphoma in a hamster colony in Knoxville.

Oncogenic viruses are probably agents which have caused very old latent infections and have been transmitted from one generation to another perhaps for centuries. The infection presumably has remained in most instances submerged, invisible and unrecognized, except for the appearance of an occasional cancer or leukemia in one of the carrier hosts.
Oncogenic viruses differ also from the virus-like agents that cause "slow virus diseases" in that they are much more susceptible to heat and to inactivation by chemicals. They cross

species only occasionally and under limited experimental conditions. In contrast, all slow virus diseases have certain features in common: they affect the central nervous system, inducing degenerative changes in the neurons and in the gray matter without evident inflammatory changes. They are caused by filterable agents that are unusually resistant to heat, are relatively resistant to formaldehyde, can tolerate large doses of ultraviolet and ionizing radiation, cause slowly progressive diseases, and can be transmitted to monkeys and a variety of laboratory animals by inoculation of brain or other organ extracts at very high dilutions.

Creutzfeldt-Jakob disease (C.J.D.) and Scrapie

Clustering of C.J.D. cases has not been found in the U.S., but reports from other countries indicate that such does occur. About 15% of the cases are of the familial type which may suggest a genetic susceptibility to infection. It remains to be determined whether the agent of C.J.D is maintained only by patient to patient transmission, is associated with zoonotic infestation or causes widespread latent infection of man that is only rarely activated. The C.J.D. agent may turn out to be very similar to the scrapie agent which is believed to be a very small nucleic acid molecule, possibly the first viroid to be discovered in animals. Viroids are known to cause a number of diseases in plants. They consist of a small molecule of ribonucleic acid (RNA), that is smaller than the size of the nucleic acid found in conventional viruses, and does not have the protein coat that normally covers viral nucleic acids.

An obscure disease of sheep called "scrapie" has been an important subject of research. Transmission studies and neuropathological examination of brain tissue suggest that scrapie is a prototype for the spongiform encephalopathies of man, i.e., Kuru and Creutzfeldt-Jakob disease.

The discovery of the chemical nature of the scrapie agent by scientists might throw some light on the character of agents causing related brain diseases in humans, including C.J.D. and Kuru. The symptoms and pathological changes occurring in the human diseases closely resemble those of scrapie. It may be discovered that the agents causing these diseases are actually a variant of the scrapie agent which can be transmitted to humans who eat scrapie-contaminated sheep brains. Moreover it is suspected that similar agents may cause other, more common brain diseases including Parkinson's disease.

The major objective of a research project at Yale University is to study the pathogenesis of experimental Creutzfeldt-Jakob disease in laboratory guinea pigs, hamsters and mice. Light and electron microscopic (E.M.), virological, tissue culture and biochemical techniques are utilized. The leading hypothesis is that the C.J.D. agent is composed of various strains with distinct incubation periods which cause lesions having characteristic distributions. A second hypothesis is that C.J.D. is a variant of the scrapie agent.

Cells from C.J.D. infected brains may be used to establish tissue culture lines, which die after 50 passages in vitro. Furthermore, tissue culture cells arising from C.J.D. brains are capable of occasional growth on soft agar, unlike normal brain cells which formed no colonies. The attempts, however, to produce tumors with the C.J.D. tissue culture cells by injecting them subcutaneously into immunosuppressed animals and nude mice have failed.

The role of scrapie virus in aging and other conditions, is being studied by an investigator at New York State Department of Health by the intraperitoneal inoculation of neonatal mice with scrapie virus. The results may shed light on human presenile dementia and may have implications in the spongiform encephalopathies. A complex interaction has been discovered between concurrent infection by lymphocytic choriomeningitis (LCM) and scrapie in the same animal. LCM super-infection of mice, which were also infected with scrapie, was proposed as one means of interaction with the T lymphocyte cell system during early build-up of scrapie spleen titer following intraperitoneal inoculation. It was found that not only has the incubation period lengthened, but some mice are apparently spared from scrapie death by the intercurrent LCM superinfection. This effect depends upon the interval between the scrapie and LCM inoculations.

Unexpectedly, at a certain point in time in the scrapie/LCM infection, an opposite effect occurs, whereby the scrapie incubation period is shortened to the point where intraperitoneal inoculation gives a shorter incubation period which is very similar to that expected from an intracranial inoculation. Thus, we have tenative, though unconfirmed, data which suggest that an LCM infection of the brain, occurring during an early period of scrapie intraperitoneal incubation, can convert the infection into an intracranial one, with early fatal results. One may postulate that this phenomenon may occur in human C.J.D. Further, it is conceivable that human C.J.D. only occurs if an otherwise harmless visceral infection is converted into an intracranial one, by an intercurrent mild viral (or other) encephalitis. This concept may be operative in the explanation of the mystery of the infective origin of C.J.D. in man, plus the low incidence of overt disease. By the same token, the phenomenon may be relevant to Alzheimer's disease.

There is also intensive research directed, in part, toward understanding the "slow" nature of the scrapie agent. Because the present assay for scrapie requires determination of an endpoint by titration in mice over a nine month period, it is especially tedious to purify the scrapie agent and use this preparation to study its chemical and immunological properties. The purification and subsequent elucidation of the chemical structure of the scrapie agent promises to bring new concepts and techniques to several areas of molecular biology and medicine.

The collaborative experiments conducted by investigators at the University of Wisconsin and the University of California at Riverside support the hypothesis that scrapie is caused by a viroid-like agent. The buoyant density of the infectious agent suggests that the scrapie-specific DNA is bound to and protected by another macromolecule, probably a protein and thus is a viroid varient. No one has yet been successful in adapting this neuropathic agent to a cell culture system. Cell line SHB retains a constant level of infectivity if cell replication is arrested, whereas, cells allowed to continue dividing, gradually lose infectivity. However, there is no indication, for at least 35 days, that the scrapie agent is actually replicating in these arrested cells. When SHB cells and others called HN-Jci cells were pretreated with nerve growth factor (NGF) before exposure to scrapie, NGF appeared to have no effect on the ability of the SHB cells to support scrapie replication, but the HN-Jci cells contained 100 times less infectivity when bioassayed 14 days post-infection than did untreated cells. These results may have been due to the observed toxic effect of NGF on these cells.

A retinopathy was also reported in scrapie-infected hamsters, which may be directly induced by the agent rather than as the result of retrograde degeneration from central neural damage. The higher titer of infectivity in the optic nerve at each interval tested suggests that the retina is infected via nerve fibers from the brain, centrifugally. The possible migration of infectivity in nerve fibers is also a reasonable explanation for the previous findings of infectivity in corneal epithelium in TME - infected hamsters.

Experiments on subhuman primates also indicate that scrapie-like agents can be reisolated rather easily after passage in subhuman primates. This contrasts sharply with human C.J.D. tissue which is not readily pathogenic for laboratory rodents. These results do not support speculation that C.J.D. is caused by humans becoming infected with sheep scrapie.

Herpes Viruses

The long term research goal at Sloan Kettering Institute is to define the pathogenesis of acute, latent, and reactivated herpes simplex virus (HSV) infections of the autonomic nervous system. Principal attention is directed at: a) the intrinsic properties of autonomic neurons which determine their variable capacity to support either productive or latent HSV infection; and b) the cellular metabolic consequences of acute, latent and reactivated HSV infections of the autonomic nervous system. To achieve these objectives three experimental systems are being employed: 1) an in vivo model of autonomic infection in the mouse whereby the superior cervical ganglion (SCG) is infected after intraocular viral inoculation; 2) a cell culture model using primary dissociated SCG neurons from newborn rat; and 3) an additional cell culture model using the PC12 pheochromocytoma cell line which undergoes neuron-like differentiation on exposure to nerve growth factor (NGF).

These studies promise to provide insight into the pathogenesis of HSV infections of neural tissue. The importance of HSV-neural interaction lies in the critical role of infection in determining latency and reactivation in recurrent HSV-1 (cold sores, keratitis), HSV-2 (genital herpes) disease, as well as the encephalitides caused by these viruses in both the adult (HSV-1) and neonate (HSV-2).

Recent studies provided evidence of the importance of herpes simplex virus (HSV) thymidine kinase (TK) expression in infections of trigeminal ganglion neurons. This is significant in considering the mechanisms of establishment of latent HSV infections of sensory ganglia. Such information is important in understanding latent infections of the nervous system as well as specific herpetic diseases.

From the investigations of virus replication in vivo after inoculation with TK^+ or with TK^-HSV it is apparent that HSV TK expression is important in the establishment of neuronal infection of sensory ganglia. Since these cells are the site of most latent HSV infection in experimental animals and in humans, this observation is important in the consideration of HSV pathogenesis in humans. Latent human HSV infection is significant in the understanding of recurrent herpes infections and probably HSV encephalitis and may be important in understanding neoplastic and degenerative diseases. The current interest in the clinical use of acycloguanosine, an inhibitor of TK^+HSV, is in accord with observations of the importance of HSV TK expression in the pathogenesis of HSV infections.

An investigator at the University of Minnesota is also studying herpes simplex virus infections of the nervous system. He has largely defined the progression of the infection as it moves from a peripheral site of infection through the peripheral nerves via axoplasmic flow, to the sensory ganglia, into the spinal cord and finally to the brain. This progression can be altered at the sensory ganglia where the virus can establish a latent infection in the neurons. To exploit the greater control which can be exercised in a tissue culture environment, a multi-organ culture model of rat skin and dorsal root ganglia was developed. Initial efforts were devoted to characterizing the ultrastructural and electrophysiological aspects of this model. The same parameters will be examined after MacIntyre strain of HSV infection of the cultures. Finally, the effects of various components of the rat's immune system (antiviral antibody, complement, interferon, rat "T" and "B" lymphocytes, and macrophages) on the pathogenesis of the virus will be determined.

Thymidine kinase Herpes Simplex virus studies by an investigator at Milton S. Hershey Medical Center are aimed at the demonstration of the importance of HSV TK expression in the establishment of ganglionic infection. Viral TK function was not important for ocular infection (a site of dividing and potentially dividing cells) whereas for infection of nondividing neurons, TK function was important. These results demonstrate the role of viral function in infection and are of significance in considering the pathogenesis of HSV infections.

The ultracentrifugal inoculation (UCIN) procedure is a valuable means of enhancing HSV infectivity, apparently by concentration of virus onto monolayer cells. Trigeminal ganglion studies support the contention that the latent HSV infections are non-productive. Details of the UCIN procedure have been explored and it appears to be a procedure which may be of great value for the isolation of low levels of infectious virus in experimental and possibly also in clinical situations.

Mutant Viruses

Studies of temperature sensitive 472 chandipura virus (CV) infection of mice have revealed that this mutant produces striking primary demyelination when inoculated into 3 to 4 week old Swiss mice.

An investigator at Northwestern University is working on a system that may be an important model for certain human diseases, such as ALS or MS. Inoculation of 3 to 4 week old BAlb/c mice with temperature sensitive (*ts*) G41 vesicular stomatitis virus (VSV) produced a subacute neurological disease characterized by weakness and hind limb paralysis in 90% of the mice. These clinical findings lasted from 8 to 28 days postinfection. Only 10% - 15 % of the mice died as a result of infection, and almost all show that virus recovered from these infected mice was *ts* and by co-cultivation isolatable for up to 3 to 4 weeks in brain and spinal cord tissues. These studies lend strong support to the hypothesis that *ts* mutants of VSV possess not only the capacity to attentuate *in vitro* infection but also to produce subacute to chronic central nervous system (CNS) disease. The implications for human diseases are obvious and important.

Studies of Virus-Tissue Interactions

The overall objectives of an investigator at the University of Southern California, are to study the effects of viral infection on spinal cord-muscle tissues *in vitro* from developmental, functional and metabolic points of view. Factors which might influence the susceptibility and outcome of viral infection in spinal cord-muscle cultures are studied. Recent work supported by this grant has been centered on improving culture methods for motor neurons and defining the neuronal infection by avian encephalomyelitis virus (AEV).

Very little is known about the interaction of papovaviruses with human hosts, although these agents are ubiquitous in human populations, have a definite role in the lethal central nervous system infection, progressive multifocal leukoencephalopathy (PML), and have a possible role in human neoplasia. In particular, little information exists as to the natural route of transmission of papovaviruses, the character of the initial infection which these agents produce, and the ability of these agents to produce persistent infection. Because papovaviruses have strict species-specificity, it has not yet been possible to answer these questions using human papovaviruses in laboratory animals.

Studies undertaken by an investigator at the University of Virginia hopefully applicable to human disease, have evaluated the biologic behavior of a papovavirus, K virus, in its natural host, the mouse. Experiments to date, designed to minimize erroneous data caused by contamination with other mouse viruses, have delineated the natural route of inoculation and distribution of infection for a member of the papovavirus group. Data indicate that the papovavirus regularly involves the central nervous system of its natural host during acute infection and is capable of persisting in brain and other organs for protracted periods of time despite the development of high titers of specific antibody. In addition, studies have shown that immunosuppression results in reactivation of infection and involvement of brain. These findings raise questions as to whether similar involvement of brain may occur during other papovavirus infections of animals and man.

Studies of localization of viral antigens in infected spinal cords have been very successful. Both immunofluoresence studies at the light microscopical level and immuno-peroxidase studies at both light and ultrastructural levels have been performed. The first localization of virus is in the large neurons of the anterior horns of the spinal cord starting at 4 days after infection. The virus is then transported to the terminal portions of neuronal processes and remains in preterminal axons, dendrites and postsynaptic terminals for as long as seven months. About one week after inoculation, astrocytes also become infected, and they are probably the cells which carry the disease into the white matter. In white matter, astrocytes, mononuclear cells, and especially macrophages, are the types of cells which are able to maintain the virus for months. These studies are the first demonstration of the anatomical basis of virus persistence for a picornavirus. It is particularly interesting that macrophages are collaborating with other cells in the maintenance of persistent infection. These data add support to the contention that macrophages do not simply act as scavenger cells, but actively participate in the production of disease.

Demyelinating Viruses

It is currently believed that multiple sclerosis (MS) may have a combined viral-immune cause. For this reason, animal models of virus induced demyelination have gained popularity during the past few years. Theiler's model has the advantage of being one of the few models in which virus appears to produce demyelination through the host-immune response. In addition, it is the only combined viral-immune model to be characterized by a chronic course, thus approaching the characteristics of human MS. Studies are underway at Northwestern University to investigate the pathogenesis of myelin injury in this model from different points of view, i.e. morphologically, virologically, immunologically and biochemically. Information gathered from these studies could be important for understanding the mechanisms of myelin destruction which may be operating in humans during the course of MS.

At Cornell University, explanations are being sought for the ability of canine distemper virus (CDV) to cause persistent brain infection and demyelination in dogs. These studies are undertaken with a view to study an animal model of subacute sclerosing panencephalitis and possibly other demyelinating diseases such as multiple sclerosis. Three strains of CDV that differ in their capacity to induce subacute encephalitis in specific pathogen-free (SPF) beagles were singled out for this study. Explanations are sought in these studies for the ability of CDV to cause persistent infection and demyelination in dogs. By comparing experimental allergic encephalomyelitis (EAE) with CDV induced demyelination in dogs, emphasis is placed on the importance of persistent virus in early demyelination which could be followed by an autoallergic reaction later.

If the importance of persistent virus in the initiation of demyelination can be established, the next question to ask would be: what causes the virus to persist? By studying interferon levels in serum of dogs after infection with different CDV strains, it may be possible to differentiate between infection with an attentuated (no interferon) versus virulent (injected with interferon) C.D.V. In contrast, interferon was present in CSF of dogs with persistent brain infection for extended time periods. It is not yet known whether this phenomenon represents a cause or is a result of persistent infection; however, it might serve as a marker for persistent CDV brain infection.

Lymphocyte mediated immune responses require further study before their importance in viral persistence can be evaluated. They appear to correspond with humoral antibody responses and may not be significant markers. The study of antigenic differences in CDV strains and the immune response to them in relation to persistent infections has only begun. Progress has been made in production and partial purification of dog interferon. When more purified interferon becomes available new in vivo and in vitro studies will be initiated to establish its significance in induction of persistent infections.

Canine Distemper Virus is also being studied by an investigator at Ohio State University. The overall objective of this project is to utilize the CDV as a model to study the pathogenesis of virus-induced demyelinating encephalitis as it may apply to subacute sclerosing panencephalitis (SSPE) and multiple sclerosis (MS) in man. The study is directed toward elucidation of persistent neurological infection by CDV in germ free dogs utilizing morphological, virological, immunological and biochemical approaches.

Studies are also designed to increase our understanding of the mechanisms of demyelination induced by R252-CDV. Of particular importance is the 21-day pathogenesis study. Results indicate that, for the first time, it is possible to induce reliably persistent infection and accompanying demyelination with an incidence approaching 100%. This break-through will permit careful sequential analysis of developmental aspects of this lesion and its associated immunological and virological correlates. The combined viral and immunological studies are valuable adjuncts to the in vivo studies in that they will permit further dissection of factors responsible for persistent CNS infection.

Visna is a demyelinating disease in Icelandic sheep caused by a virus. One of the most interesting aspects of persistent visna infection is the phenomenon of antigenic drift. In the context of visna, drift refers to the isolation of virus variants from chronically infected sheep which differ from the infecting virus in that they can escape neutralization by antisera which neutralizes the strain used for infection.

Several tentative conclusions are suggested: a) the occurrence of variant viruses is confirmed; b) variants probably play no essential role in persistence since parental serotypes co-exist with variants; c) variants could play an important role in occurrence of lesions and clinical disease, but this remains to be determined; d) the development of a hybridoma system is clearly justified, since there are enough variant viruses to deserve analysis.

Recent light microscopic studies by investigators at the University of Pennsylvania have clearly indicated that the pathological lesions of clinical visna are markedly different from those seen in subclinical infections. Subclinical visna is essentially a chronic encephalomylitis. When clinical disease appears there are severe focal lesions of spinal cord and brain stem, in which tissue destruction, scarring, and demyelination are prominent. Since the Icelandic sheep model is the only one in which clinical disease occurs, it offers a unique opportunity to describe the demyelinating lesion of visna at an ultrastructural level. To do such a study, it is necessary to perfuse living sheep with fixative, remove CNS tissues, and cut slices in a vibratone for examination by Nomarski interference optics. Sections with lesions are then processed for electron microscopy.

Most of the studies in Icelandic sheep have employed strain 1514 of visna virus. Although this produces some clinical cases, the 5-year cumulative attack rate is less than 20%. To attempt to identify a more virulent strain, an isolate (1522) from the choroid plexus of an acute case was inoculated intracerebrally and a subsequent acute case (1759) used as the source for another isolate. Both 1522 and 1759 strains are now being tested for their virulence. Recent CSF studies have shown that about half of the Icelandic sheep with chronic visna infection have oligoclonal bands in the CSF.

Newer Techniques

An investigator at the University of California, San Francisco, is studying the synthesis of visna virus nucleic acids. This work is directed toward elucidation of the molecular basis for the persistence of the virus, and the slow development of disease. The current hypothesis is that persistence and the course of the disease may be explained by restriction in virus gene expression in infected tissues. This analysis of necessity requires methodology which will quantitate synthesis of viral DNA and RNA in cells in tissues. For this reason considerable effort has been devoted to in situ hybridization, and it is possible now to assess viral RNA synthesis at single copy levels in cells. Studies in progress are aimed at increasing the sensitivity of the assay for DNA to comparable levels, and to developing an assay for viral proteins that is both quantitative and more sensitive than immunofluoresence. With these methods they can determine on what level virus gene regulation is affected in vivo. In particular they think that these experiments will demonstrate that virus production is regulated under both restricted and permissive conditions of replication by gene dosage effects.

In order to detect viruses as sensitively as possible, an investigator at the Center for Neurologic Study has: (a) developed methods to produce various radioactive viral nucleic acids to be used as probes to specifically detect the presence of certain viruses in the CNS tissue; (b) modified nucleic acid hybridization methods in order to increase the sensitivity of virus detection; and (c) made basic discoveries in the area of nucleic acid hybridization which should allow an increase of the sensitivity of viral detection by 100-1000 times. The modified test currently used will specifically detect the presence of one copy of virus RNA per 300 cells when one gram of tissue is used in the assay. The best radioimmune assays will detect about 10-15 micro-moles of virus RNA while the hybridization method is 10-100 times more sensitive. These methods will be used to examine multiple sclerosis, amytrophic lateral sclerosis and Parkinson's disease tissues for the presence of measles, polio and influenza viruses respectively. These viruses have been implicated in these diseases.

Guillain-Barre Syndrome

Idiopathic polyneuritis, known as Guillain-Barre syndrome (GB) is, since the advent of vaccination against poliomyelitis, the most common cause of acute severe generalized paralytic disease in man. Although a relatively common condition affecting the population at a reported annual prevalence of 1-1.6 cases per 100,000 population, it has recently come to public attention in the United States as a presumed complication of vaccination against "swine flu". Several grantees are investigating possible cause-effect relationship in this syndrome. Relationship of allergic neuritis (EAN) to GB is studied because GB patients' lymphocytes respond to myelin P2 protein. This further bridges the gap between EAN and GB and suggests a prime event in the human disease may be sensitization to P2 protein, probably initiated by a viral infection. Relevant research conducted at Sidney Farber Cancer Institute is to examine the relationships between determinants of the major histocompatability complex of man (HLA), swine flu immunization dependent immunological phenomena, and the presence or absence of the Guillain-Barre syndrome. Advantage is taken of the expertise of this laboratory in the immunogenetic analysis of experimental auto-immune neurological disease, the study of thymus derived cell function, and precise indepth studies of HLA.

Treatment of Viral Infections

Some viral infections can be treated. There are a few promising antiviral agents currently under study. Adenine arabinoside (ara-A) may be useful in the treatment of viral diseases such as fever blisters caused by herpes simplex virus, chicken pox (varicella), salivary gland virus infection caused by cytomegalovirus, shingles, and small pox caused by vaccinia viruses. Interferon may or may not become one of the most widely used drugs to combat viral diseases as well as various cancers. Interferon reduces the pain and spread of the lesions caused by herpes zoster. It also may be effective in preventing herpes varicella in children suffering from leukemia. The results were encouraging when patients were treated with a combination of interferon and ara-A.

Amantadine was found to be helpful in reducing the duration and severity of symptoms of influenza infection. Other drugs under study with potential for treatment of viral infections are: ribavirin, phosphonoacetic acid, phosphonoformic acid, bromovinyl deoxyuridine, arildone, and 2-Deoxy-D-glucose.

Bacterial Infections

Bacterial meningitis remains a very significant problem in the antibiotic era. This disease has increased in the past several years and in particular, a striking increase in infection due to Hemophilus influenzae, type b, has been observed. Recently, an increased incidence of meningitis due to Group B beta hemolytic streptococci in children over 1 month of age but less than 6 months of age has been observed. There are selected clinical and laboratory findings that one can detect at the moment of admission that permit prediction of the likelihood that any given patient may experience sequelae of meningitis.

The studies at Johns Hopkins University have expanded previous observations on the pathogenesis of H. influenzae b meningitis in the infant rat model. Since prevention of H. influenzae type b invasive disease is the ideal way to protect children against the serious morbidity and mortality resulting from meningitis, the use of the infant rat provides an approach to exploring the induction of protective immunity on an experimental basis. Although caution must be exercised in extrapolation of data from animals to man, a valid experimental model can provide information that cannot be readily obtained by other approaches.

Studies of bacterial meningitis caused by Hemophilus influenzae, in children, at Baylor College of Medicine, document in a prospective fashion, for the first time, that prior treatment with antibiotics should not preclude making a specific etiological diagnosis of meningitis, provided a complete evaluation of cerebrospinal fluid is performed, coupled with concurrent analysis of blood, CSF and urine utilizing countercurrent immunoelectrophoresis.

A high frequency of inappropriate secretion of antidiuretic hormone during uncomplicated bacterial meningitis has been documented. In particular, specific measurements of antidiuretic hormone concentration in serum and CSF in children with bacterial meningitis have been made for the first time. This data, coupled with finding that hyponatremia correlates significantly with various sequelae of meningitis should lead to more intensive and aggressive ancillary measures designed to limit excessive fluid administration. It is hoped that the future studies may reveal ways in which antidiuretic hormone (ADH) secretion can be altered therapeutically.

In conclusion, these studies have demonstrated that appropriate early and vigorous treatment of the patient with bacterial meningitis can limit both neurologic and psychological sequelae of the disease. The studies also have demonstrated the requirement for very careful control of fluid balance as an important adjunct to the therapy of patients with bacterial meningitis. The utility of countercurrent immunoelectrophoresis as a routine procedure for rapidly establishing the etiologic agent of the infection has also been demonstrated.

MUSCULAR AND NEUROMUSCULAR DISORDERS

This section of the Neurological Disorders Program supports research in basic nerve and muscle function and dysfunction with special emphasis on Muscular Dystrophy, Myasthenia Gravis and Peripheral Neuropathies. In July 1981, 152 grants were active, including four program projects, one for basic research in neuromuscular diseases, two clinical research centers, one for neuromuscular disorders and one for peripheral neuropathies, and a collaborative clinical trial on the use of plasmapheresis for the treatment of Guillain-Barre syndrome. Total cost for these activities was $13,756,544.

Basic Studies on Nerve and Muscle

Nearly 50% of the funds of the grant portfolio are devoted to basic research on nerves, muscles and their interactions. These studies utilize a wide variety of preparations from simple invertebrate organisms through amphibia, small mammals and humans. Physiological, biochemical anatomical and molecular biological techniques are being used to determine the macromolecular basis of muscle contraction, the mechanism of excitation contraction coupling, and the function of the muscle spindle system. Studies on nerve itself are also underway to specify the channels, gating mechanisms and ion selectivity involved in nerve conduction. In addition, the program supports work on nerve-muscle interaction. A large number of investigations are devoted to determining both the pre- and postsynaptic events involved in neuromuscular and synaptic transmission. These include the mechanism of transmitter action, storage, release and recycling of synaptic vesicles. The activity of acetycholine receptors and the enzyme anticholinesterase are being examined as well as the changes that can be induced in the efficiency of synaptic transmission. Finally, both the control of contraction by recruitment and rate coding in reflex and voluntary motion and the trophic effects exerted by nerve and muscle upon each other are under investigation.

Invertebrates, with simple nervous systems, large neurons and stereotyped behaviors are exceptionally useful for physiological, anatomical and biochemical studies to determine the cellular and eventually the molecular basis of behavior. The central nervous system of the lobster has proven to be a valuable model for studies aimed at understanding the chemical basis for the differences between neurons that underly their physiological functions. The neurons are large, relatively few in number and the axons and cell bodies of single physiologically identified nerve cells can be isolated repeatedly from a series of animals. This allows detailed chemical and physiological analyses on single types of functionally identified neurons. Gamma-amino butyric acid and glutamic acid have been identified as the transmitters at the neuromuscular junction and acetylcholine is the probable sensory transmitter compound. The actions of several biogenic amines are also being investigated in an attempt to analyze the neurosecretory system, in detail, from the level of its activation to its effect on lobster behavior. This study of the neuronal basis for a complete behavior may shed light on the function of such systems in more complex organisms since, based on neurophysiological and chemical evidence, similar mechanisms operate in both invertebrates and in higher mammals.

Tissue and organ culture is another way of simplifying the mammalian nervous system for easier analysis. Developmental changes have been monitored during the formation of neuromuscular contacts between embryonic frog neurons and myotubes derived from a rat skeletal muscle cell line. This system is providing information on the specificity of neuronal contacts. It has also been demonstrated that fetal spinal cord can be co-cultured with adult skeletal muscle to form functional nerve muscle junctions with anatomical and physiological properties of the *in vivo* preparation. This system is now being used to investigate normal function as well as the effects of disuse and denervation atrophy.

The development of freeze fracture techniques has made it possible to examine the insides of cell membranes under the electron microscope. Combining this method with more traditional thin sections and specific affinity labeling techniques has allowed biochemical functions to be assigned to individual classes of intramembraneous particles like the acetylcholine receptors at the nerve-muscle junction. Freeze fracture and immunocytochemical studies on the axons of the tadpole at various developmental stages have indicated that the intramembrane particles located at the nodes of Ranvier are likely to be sodium channels and are responsible for the excitability of the nodal membrane.

The mechanism of synaptic transmission, exocytosis and endocytosis of membrane is being studied in a mutant fruit fly, where control of the temperature of the animal with a thermoelectric device can be used to cause reversible depletion of vesicles and block membrane recycling. Electron microscopic study revealed that the structure of the neuromuscular junction of the mutant shi is no different from that of normal fruit flies at room temperature but at high temperature (29,C) there is almost complete depletion of synaptic vesicles and formation of cisternae in the terminal. These investigations should provide fundamental data on synaptic transmission that has been unobtainable with other preparations which require the use of pharmachological agents of only partially defined specificity and lack of reversibility.

Investigations on the role of calcium in muscle contraction continue to yield new information. Electrical stimulation of skeletal muscle fiber leads to the release of calcium stored in the sarcoplasmic reticulum which then activates muscle contraction. This work utilizes the frog muscle, and the investigators have shown that the sarcoplasmic reticulum senses the tubular membrane potential by charge movement alone. New optical dyes are being designed to measure both membrane potentials and the amount of free calcium present in muscle cells during activation, since the previous optical measurements have been demonstrated inaccurate due to the intraction of the dyes with the living system.

The muscle spindle is a small sensory organ of muscle that both receives and sends information to the central nervous system about the length and tension of the muscle fibers within which it is embedded. Compared to the neuromuscular junction, little is known about the transduction processes at these sensory terminals. Recent experiments indicate that physical distortion of parts of the spindle membrane result in the opening of ionic channel gates, a movement of charged particles and the generation of the receptor potential. Studies are underway to determine the alterations of this process in diabetic neuropathy, hypertrophic polyneuropathy and anterior horn cell disease in mice and in humans and during regeneration of spindles in grafted muscle. In addition, muscle spindle, capillaries provide an easily accessible model system to study the blood-nervous system barrier since transport of material from the blood across the endothelial cells of the blood-brain barrier has been difficult to study *in vivo*.

Although it has been known for some time that both the nerve and the muscle are affected when their normal interaction is interrupted, the causes of these changes have only been recently documented. Studies utilizing chronically implanted tetrodotoxin filled cuffs to block impulse conduction in both sensory and motor nerves have demonstrated that the primary factor responsible for the maintenance of motoneuron properties is the normal metabolism of the innervated muscle rather than the contractile activity. Conversely, denervated skeletal muscle has been shown to have stimulated transcription of nuclear RNAs and increased phosphorylation of cytosolic and nuclear proteins. Furthermore, and very relevant to recovery from injury, restoration of central synaptic function following peripheral nerve damage requires mechanical contact of the nerve with the muscle rather than the electrical activity of the motor or sensory fibers.

Finally, work is underway to develop a computer assisted image analysis system to make quantitative morphometric evaluation of nerve and muscle fibers more accurate, less tedious and hence more available for research and clinical applications.

Muscular Dystrophy

Muscular dystrophy is a group of chronic, progressive, genetically determined diseases characterized by weakness and wasting of the voluntary muscles. The rate of progression varies markedly from type to type. It is estimated that some 200,000 men, women, and children in the United States are suffering from some form of this disease. Nearly two-thirds of the known victims are children between the ages of 3 and 13. There is no effective treatment for muscular dystrophy itself. To date, none of the wide variety of diets and drugs administered to patients has shown a significant or lasting effect on the course of the disease. Physical therapy has limited value in delaying contractures but does not otherwise affect the course of the dystrophic process. Antibiotics may prolong the lives of children who would otherwise succumb to respiratory infections. In July 1981, 24 grants providing $2,975,748 were active in the Muscular Dystrophy sub-program, including one program project.

Duchenne muscular distrophy (DMD) is the most common and best defined of these disorders. It is an inherited recessive trait transmitted by clinically unaffected females almost exclusively to their male progeny which usually results in the affected boys being unable to walk by the age of 10 and rarely surviving beyond the age of 20. A possible cause of DMD, as for other genetically transmitted diseases, is a single gene mutation that results in a defective or absent enzyme or a small group of similar enzymes. Many workers in the field are therefore examining the possiblility that the primary biochemical lesion in muscular dystrophy is manifested as a generalized defect in cell membranes in addition to the known alterations in skeletal muscle.

In Duchenne's dystrophy, the affected striated muscle is characterized by the presence of scattered foci of degenerating myofibers. Within these foci, numerous myogenic cells in various stages of regeneration represent the potential of the muscle for repair. In older, patients, the process of muscle regeneration becomes abnormal and eventually has no influence on the clinical progress of dystrophic degeneration. Work begun to test the hypothesis that the later regenerative failure is due to a direct effect upon the myogenic stem cell revealed that, contrary to established opinion, induction of muscle competence in somites is a two phase process. First the myotome is induced and gives rise to a post mitotic contractile rudiment. Then proliforatory stem cells (myoblasts) arise which ultimately develop into musculature. These latter cells are derived from the dermatome. A myoblast-fibroblast modulation is proposed to account for the characteristic loss of regenerating stem cells and the simultaneous increase in interstitial fibrosis and developmental studies to verify this are underway.

A potential connective tissue-microvascular contribution to a possible ischemic etiology of muscular dystrophy has been brought to light by ultrastructural examination of muscle biopsy material which show a reduction in the vascular network in addition to the characteristic increases of the connective tissue matrix. Up to one third of the feeding capillaries were eliminated in dystrophic foci from patients with Beckers and Duchenne Dystrophy.

The decrease in a lysosomal enzyme noted in cultured human fibroblasts from DMD patients has been shown to be secondary to some more fundamental change in the lysosomal membrane, abnormality in chloride permeability resulting from abnormal lysosomal membrane proteins.

This membrane hypothesis has received particular support in the case of the myotonic disorders. There is evidence of biochemical abnormalities in the muscle sarcolemma and red cell membrane in patients with myotonic dystrophy, and there are convincing data that the myotonic phenomenon itself is due to a conductance abnormality in the surface membrane.

A diffuse decrease of internal membrane particles has been demonstrated in Duchenne dystrophy using freeze-fracture techniques. Expression of this defect in cultured muscle cell would be of considerable interest because it would indicate a genetically determined abnormality inherent in the muscle cell, possibly, in the plasma membrane. Erythrocyte membrane properties of DMD patients are also being studied by biophysical methods.

In addition to the work described above on human tissue, hereditary muscle disease, closely resembling human muscular dystrophy, has appeared in a number of animal species, including hamsters, chickens and rats. These animal models allow scientists to perform controlled experiments which are impossible to carry out on human beings

The genetically dystrophic chicken is being utilized to develop a beneficial form of chemotherapy. Muscle cells from embryonic chickens are grown in a culture to provide an in vitro assay system in which to study the potential efficacy of specific classes of drugs with various modes of action upon muscle growth, protein turnover and cytochemistry. Inherent practical problems which have impeded the intensive description of muscle growth and protein turnover with drug intervention in whole muscle from intact animals are circumvented with this new technique.

At the University of Pennsylvania there is a program project of multidisciplinary studies of various muscular disease. Studies utilizing a drug induced goat model of myotonic dystrophy have shown that the alteration in the physical properties of muscle membrane due to an increase in desmosterol concentration in restricted to the hydrophobic core of the membrane. Electrophysiological data suggest that the repetitive firing of the membrane is due to an enhanced sodium conductance and that the prolonged contractions are not due to an abnormality of calcium reaccumulation in the sarcoplasmic reticulum, as had previously been suspected.

Myasthenia Gravis

Myasthenia Gravis (MG) is a chronic neuromuscular disorder characterized by progressive weakness and abnormally rapid fatigue of the voluntary muscles. Twenty years ago about 30% of the patients died within 2-4 years of contracting the disease and many of those that lived were severely disabled. Today mortality is less than 5%, and many patients can live relatively normal lives despite the presence of the disorder. In July 1981, 15 were active in the MG subprogram, totaling $1,444,489.

Basic research on MG has utilized such diverse animals as electric fish whose electroplaques produce relatively large quantities of acetylcholine receptors, snakes that produce toxins which specifically bind to these receptors, and rats immunized against purified acetylcholine receptors that develop symptoms much like humans having the disease. A radioimmunoassay was developed for detecting antibodies against acetylcholine receptors and utilized to find them in animals immunized against purified acetylcholine receptor. Using this assay, it was possible to detect antibodies against human acetylcholine receptor in sera from patients with myasthenia gravis. These studies have demonstrated that the symptoms of MG result from a decrease in the acetylcholine receptors of skeletal muscle motor-end plates caused by an immunologic abnormality.

The objectives of most of the projects relevant to myasthenia gravis are to determine mechanisms governing the synthesis and assembly of the acetylcholine receptor, to understand the structural basis of acetylcholine receptor function and to elucidate the pathological mechanisms of the disease. Experimental autoimmune myasthenia gravis induced by immunizing animals with purified acetylcholine receptor, is being studied as a model for human MG.

Immunological studies have shown that both a humoral and cellular immune response are involved in the experimentally induced disease. Ultrastructural studies of the motor end plate in rats immunized with acetylcholine receptor have demonstrated postsynaptic degeneration and the formation of simplified postsynaptic regions resembling the situation found in human myasthenia gravis. Physiological studies have shown that diaphragm muscle taken from immunized rats has a reduced sensitivity to iontophoretically applied acetylcholine.

The muscle weakens and fatiguability in myasthenia gravis are now generally believed to be a consequence of an auto immune-mediated reduction in the amount of acetylcholine receptor at the voluntary muscle endplate. However, although antibodies have been directly implicated in the pathogenesis of myasthenia gravis, the relation between the presence of antibodies and impairment of neuromuscular transmission is not a simple one. Thus, a wide range in the levels of anti-receptor antibodies is found in the sera of myasthenic patients, and the titers are poorly correlated with the severity of clinical symptoms. A possible explanation for this discrepancy is that the acetylcholine receptor is a complex antigen with many determinants, and that antisera to it are composed of a heterogeneous group of antibodies, only some of which lead to dysfunction. Carbohydrates, which can be removed ensymatically, play a signigicant role as antigenic binding sites. Selective removal techniques reduce acetylcholine receptor antigenicity against myasthenic immunogamma globulin and provide a useful tool for determining the specific form of the immune response.

A recently developed technique for making monoclonal antibodies offers an ideal tool with which to investigate the relation between antibody specificity and pathogenic effect. With monospecific antibodies it is possible to define the antigenic sites that mediate receptor modulation, and test the ability of these antibodies to induce experimental autoimmune myasthenia gravis.

A sensitive bioassay has been developed to measure serum thymic hormone levels in patients with MG. This assay is now being used to determine the relationship between altered hormone levels and clinical benefit. In the presence of MG antibodies the rate of acetylcholine receptor degradation is further increased when thyroid hormone levels are high or low. These results suggest that deterioration of MG patients with dysthyroid states may relate to effects of this hormone on receptor turnover.

Understanding the pathogenesis of the disease also requires further information about the acetylcholine receptors in human muscle. Although indirect evidence suggest that the structure of the human acetylcholine receptor is similar to that of other species, it has not been isolated. Isolation and characterization of the human acetylcholine receptor is underway. This will allow further definition of the specificity of the anti-receptor antibodies in myasthenic sera.

Several relatively successful treatments to relieve the symptoms of myasthenia gravis are presently in use. These include drugs which block cholinesterase activity, immunosuppressants, thymectomy, which removes antibodies from production and plasmapheresis, which removes antibodies from the blood. However, the specific information being obtained on the etiology of the disease should yield far more precise and effective treatment. Even more important these developments may lead to the prevention of this, as well as other, auto-immune diseases.

Peripheral Neuropathies

The peripheral neuropathies are common and serious health problems often associated with prolonged morbidity. The majority of the affected population are diabetics. There are approximately three and a half million diabetics in the United States and 10% of them have symptoms of painful burning, numbness, weakness or paralysis of the extremities. However, the most distressing neurological deficit is probably the impotence experienced by male diabetics as a result of peripheral neuropathy. The direct cause of these neurological disorders is not known, and no therapeutic measures are available. The Neurological Disorders Program especially encourages research in this area. in addition to diabetic neuropathy, the Program supports research in steroid and toxic neuropathy and in Guillain-Barre syndrome. In July 1981, 12 regular grants and one clinical research center program project in the general area of peripheral neuropathy were active at a cost of $1,952,796. In addition, portions of two other program projects, classified under different categories, devote a significant portion of their research to diabetic neuropathy.

A new project in Israel is based on the observation that hypertonic glucose causes a transient increase in the frequency of miniature end plate potentials that is prevented by insulin. In addition, the work on the insulin sensitive influx of D-glucose at the nerve muscle junction with experimental diabetes mellitus will be important not only for medicine but also for understanding synaptic action.

At the Mayo Clinic and Hormel Institute, investigators in the Peripheral Neuropathy Clinical Research Center are conducting multidisciplinary basic and clinical studies into the cause and treatment of diabetic neuropathy, heavy metal neuropathy, inflammatory polyradiculoneuropathy and inherited neuropathies. The major goals are the understanding of the mechanism of nerve fiber degeneration and regeneration at cellular, subcellular, and molecular levels, the determination of the efficacy of specific treatments, the finding of improved methods of detection, characterization, and monitoring of neurological deficits of patients with neuropathies and the understanding of the mechanisms of neuropathic symptomatology. Clinical trials of treatment of diabetic neuropathy, of inflammatory-demyelinating polyradiculoneuropathy and of dysproteinemic neuropathies are well under way. Morphometric and pathologic studies of postmortem and biopsied tissues are being done and are providing new insights into pathologic cause.

Other projects in diabetic neuropathy are aimed at understanding its pathogenesis using various animal models. An investigation of the correlation among axoplasmic transport, nerve conduction and morphology has demonstrated that changes in down flow rates can indeed be relateed to degrees of hyperglycemia. In addition, an investigation is underway on the altered protein and lipid metabolism in the peripheral nerve in diabetic rats. Finally, an electronmicrographic study of peripheral nerve basement membranes in human diabetics has revealed an almost uniform occurrence of peripheral neuropathy and a thickening of the basement membranes of perineurial and Schwann Cells.

At the muscular disease center at the University of Pennsylvania investigators have been examining a model of experimental allergic neuritis inducible in rabbits by immunization with purified galactocerbroside. This results in a clinical illness characterized by flaccid quadriparesis. Electrophysiologically there is a pattern of multifocal conduction slowing a conduction block, that resembles that of recovering human demyelinative neuropathies.

Neuropathologically, there is focal demyelination and remyelination affecting multiple sites, but especially the dorsal root ganglia.

In addition, investigations on Guillain-Barre Syndrome have demonstrated that the rat is a far more suitable animal in which to study experimental allergic neuritis, a model for the disease, than are rabbits, guinea pigs or monkeys. Furthermore, a protein of peripheral nerve myelin has been identified as the neuritogenic antigen when present as a lipid-protein complex. These studies should eventually provide the insight needed to elucidate the induction and possible suppression of the Guillain-Barre Syndrome in humans. Finally, a collaborative clinical trial on the use of plasmapheresis to treat acute Guillain-Barre Syndrome is underway and the results should be available by 1983.

NEUROLOGICAL DISORDERS OF AGING

The program currently supporting research in the neurobiology of aging is composed of five sections. These are: Parkinson's disease, Huntington's disease, Alzheimer's disease and other diseases of aging, Related Disorders, such as tardive dyskinesia, and General Studies.
Grants on Parkinson's disease primarily follow a biochemical strategy (29 grants, $3,000,000). A broadbased approach ranging across genetics, biochemistry, and psychology is being pursued in the Huntington's disease program (18 grants, $2,400,000). Research on Alzheimer's disease and other dementias of aging, which pose major public health problems, is gradually increasing. The program in General Studies includes work on the structural and functional alterations of the normal and pathological aging nervous system, (14 grants, $900,000). The Related Disorders program research projects which have pharmacological implications (2 grants, $80,000) focuses specially on tardive dyskinesis this year.

The total program contains 78 active research grants totalling $8,200,000. During fiscal year 1981 the program received 93 applications for research support, of which 13 were paid totalling $680,000.

Parkinson's Disease and Parkinsonism

Parkinson's disease, the most common form of Parkinsonism, is an illness almost unique to those over the age of 50. About one-half million people in the United States or about 1% of the population over age 50, are affected by this disease. Prevalence and incidence rates remain the same in all races and throughout the world where good epidemiological studies have been conducted. Men and women are equally affected.

Evidence to date implicating a hereditary factor in Parkinson's disease is still ambiguous. A large study of monozygotic twins, one of each set with Parkinson's disease, was conducted by investigators at Mt. Sinai Hospital in New York. That study demonstrated that in no instance were both twins of a set affected. There is also no evidence that offspring of Parkinson's disease patients have a greater risk of developing the illness than anyone else. However, some families have been identified in which multiple sibs have contracted the disease. Since husbands and wives share similar environments and there does not seem to be an increased incidence of disease among spouses, it is unlikely that a dietary or environmental pollutant is the origin.

The cause of Parkinson's disease remains a mystery. Dopamine (DA) containing neurons in the substantia nigra die, causing a depletion of this important neurotransmitter. Gradually, clinical signs of tremor, rigidity, and bradykinesia begin to appear, becoming more severe as time passes. Many patients suffer gradually diminished intellectual faculties. The symptoms of Parkinsonism can also result from neuroleptic administration, as a postencephalitic sequelae, from arteriosclerosis and from a variety of diseases and intoxications.

The majority of grants on Parkinson's disease focus on the biochemistry of the illness and the ways in which neurotransmitter systems transmit messages in the brain areas most affected. It is not surprising that the biochemistry of this disorder should preoccupy scientific attention since discovery of the deficiencies of dopamine in Parkinson's disease patients led to breakthroughs in our understanding of neurochemistry and pharamacology in brain disorders in general.

Clinical Studies

Now that the initial excitement of discovering that decreased dopamine stores leads to Parkinsonian symptomatology has subsided, it has become increasingly apparent that administration of L-dopa to increase endogenous dopamine stores is not sufficient to treat the disease completely. Unpleasant side effects and an erratic effectiveness of the treatment, known as the "on-off" phenomenon, have pushed scientists to seek new treatments. Many of these compounds act in concert with L-dopa to increase its potency; others mimic its action.

Investigators at New York University have had a long-standing research program dedicated to discovering new treatments for Parkinsonism. They have had some success using dopamine agonists such as bromocriptine and lergotrile. Both drugs were effective in relieving tremor in Parkinsonian patients and also in VMT-lesioned monkeys, but lergotrile was shown to have significant hepatotoxic effects. Several ergoline derivatives were evaluated for their dopamine agonist activity in animals, but only two drugs, pergolide and lisuride, were shown to be potent DA agonists and long acting agents in the experimental animal models. Preliminary clinical studies with pergolide appear to be positive. This project is exploring many aspects of DA receptor function, particuarly identifying DA receptor sub-types, and exploring the specificity of action of DA agonists at different DA receptors. The relationship of this neurotransmitter and its receptors to the pathogenesis and therapy of Parkinson's disease is being pursued. The nigral graft model and the possible role of epinephrine systems in DA-mediated behaviors is also being explored.

Studies are now under way at the Columbia Presbyterian Hospital to test a new therapy for Parkinsonism. Working on a theory that the adverse side effects of L-dopa treatment, including the debilitating "on-off" phenomena, stems from the conversion of dopamine to o-methyldopamines, the investigators propose to use U-0521 or other catechol-o-methyl transferase (COMT) inhibitors to prevent this conversion and serve as an adjunct treatment in Parkinsonism. These inhibitors, by inhibiting methylation of levodopa in erythrocytes, may prolong the stage of high concentrations of L-dopa in these cells, thus possibly providing a pool of available L-dopa for use by the brain. COMT inhibitors may prolong levodopa sequestration in erythrocytes and enhance the efficacy of L-dopa therapy in Parkinsonism. The investigators will further explore the role of the red blood cell as a possible vehicle of L-dopa transfer and as an agent for taking up L-dopa, activities which may account for some of the variability in blood levels of the drug. Experimentation with COMT inhibitors will be done in rats and in Parkinson's disease patients.

In order to improve the therapeutic efficacy of existing treatments for Parkinson's disease, investigators at the Illinois Institute of Technology are experimenting with the use of metal chelates bound to L-dopa as an aid to transporting the amino acid across the blood-brain barrier.

New compounds will hopefully be added to the drug armamentarium currently available for treating Parkinsonism. An investigator at St. Louis University has identified a group of carboxylic acid derivatives of tetrahydroisoquinoline compounds which have important pharmacologial effects on an endogenous opiate system on neuroendocrine systems, and on the neurotransmitters dopamine and epinephrine.

Pharmacological tools are not the only resources available for the clinical treatment of Parkinson's disease. A scientist at the University of Wisconsin is examining the clinical efficacy of a combined program of stress management and EMG biofeedback relaxation techniques to reduce Parkinsonian symptoms. Biofeedback training will enable the patient to manage specific problems, such as rigidity, tremor, and "freezing", while learning to manage stress will help the patient minimize situations which exacerbate symptoms. The study promises to develop a useful adjunct therapy with no pharmacological side effects to interfere.

Centers

At the University of Colorado a "Center for the Study of Basal Ganglia Disorders and Neurotransmitter Function" has had a continuing and productive history. Neuropharmacological, neurochemical, electrophysiological and immunocytochemical techniques are used to explore normal and abnormal functioning of the basal ganglia. The major thrust of the program is a multidisciplinary study of neurotransmitters and neuromodulators in the central nervous system (CNS) with major emphasis on the basal ganglia and the nigrostriatal dopamine pathway. Four research programs examine the neurochemical and electrophysiological changes in basal ganglion function brought about by acute and chronic nerve stimulation and agonist or antagonist drug administration. Special attention is given to the roles of presynaptic and postsynaptic receptors. The effects of chronic drug administration and, as a related theme, neuronal plasticity are the focus of a number of research projects. Studies include aspects of neuronal growth, differentiation and regeneration, and the influences of calcium dependent regulator proteins, glycoprotiens and growth factors on these processes. Neurotransmitter biosynthetic enzymes are viewed as indices of neuronal growth and development.

Clinical studies in this program attack the problem of tardive dyskinesia (TD), a troublesome iatrogenic disorder which is a pernicious consequence of prolonged neuroleptic use. Evoked and spontaneous EEG responses will be correlated with urinary biogenic amine metabolites. Clonidine and propranolol, which do not give rise to TD, will be tested as possible therapeutic agents for schizophrenic patients with tardive dyskinesia. Since patients show a variable vulnerability to develop TD, and there is at present no way to differentiate those that are at higher risk than others, investigators will attempt an intermittent L-dopa challenge in neuroleptically treated patients to see if it is prognostic of impending tardive dyskinesia.

At Yeshiva University in New York, investigators in a Center research program are also studying the role of biogenic amines in neurological disorders. Clinical and basic research studies at the Center are aimed at further elucidating the dopamine neuronal receptor system. These investigators have pharmacological evidence of three types of dopamine adenylate cyclase receptors in the striatum, anterior limbic cortex, and frontal cortex. Ligand binding studies are being carried out within parts of the extrapyramidal system to determine the properties of dopamine adenylate cyclase receptors including supersensitivity and subsensitivity. Investigations will be made of the behavioral effects in rats with denervation supersensitivity after nigrostriatal lesioning. As part of a project to study the dopamine system as a whole and its interactions with other neuronal systems, the effects on the DA neuronal system of peptide transmitters and gamma amino butryic acid (GABA) will be examined. The investigators are using a variety of sophisticated techniques including 2-Deoxyglucose autoradiography and histofluoresence to learn more about the sites of action of DA agonists and the anatomy and processes of DA cells. Clinical studies have included patients with a variety of diseases which affect aminergic activity, such as Tourette's syndrome, tardive dyskinesia, action myoclonus, and others.

Mt. Sinai School of Medicine is the home of a clinical "Center for Research on Parkinson's Disease and Allied Disorders". A multidisciplinary program of clinical and basic research focuses on clinical trials with therapeutic agents, measurement of body fluids, detailed observations of the natural history of the disease and the development of possible new treatments. A tissue bank stores autopsy brain tissue which is analyzed with a variety of histochemical and neurophysiological techniques to further identify neruophysiological and chemical pathology caused by Parkinson's disease. The role of viruses as possible etiological agents is being pursued. Basic biochemical studies focus on amino acid metabolism in the basal ganglia and on synaptology, among other areas.

Biochemistry and Pharmacology

Considering the need for better pharmacological tools to treat movement disorders such as Parkinsonism, Huntington's disease, Tourette's syndrome, and tardive dyskinesia, the discovery of the clinical efficacy of apomorphine has aroused considerable interest. An investigator at the University of Texas is continuing a program of basic research on the metabolism of apomorphine (APO) and N-n-propylnorapomorphine (NPA). These two drugs have shown definite promise as clinically useful anti-Parkinsonian agents. The investigators will continue their work developing analytical methods for studying these drugs and their analogs and in metabolites in biological material, and will pursue ways to overcome the deleterious side effects of the drugs, particularly azotemia. Studies will be carried out in the rabbit which seems to be a satisfactory animal model.

At Ohio State University a related project is being pursued. Scientists are determining the molecular mechanisms by which amphetamine causes increased synthesis and release of dopamine and how amphetamines and other CNS stimulants exert their behavioral and biochemical effects.

Rapid advances have been made in our understanding of neurotransmitters and their receptors, from the initial description of neurotransmitters to the discovery of multiple receptors for these transmitters. Investigators at the University of Colorado are exploring the densities and properties of receptors for dopamine, norepinephrine, and acetycholine in the caudate nucleus. They are looking for the possiblity of multiple sub-types of receptors for each of these transmitters and will therefore attempt to localize these receptors to their specific cell populations.

Understanding the pharmacology of the striatal dopaminergic system may yield clues to the etiology or possible treatment of Parkinson's disease. The enzyme dopamine-beta-hydroxylase (DBH) catalyzes the reaction which converts dopamine to norephinephrine through an active oxygen intermediate. An investigator at Carnegie-Mellon University is seeking to identify this oxygen intermediate and determine if superoxide radicals participate in the hydroxylation process. The study may teach us how DBH and other mono-oxygenases incorporate molecular oxygen into their substrates.

A difficulty posed by studies of the CNS has been that in order to examine certain aspects of neurotransmitter activity, animals needed to be sacrificed to obtain any data. A radiologist and chemist at the University of Chicago is using a non-invasive means of evaluating CNS dopaminergic activity by labeling bromine analogues of L-dopa and spiroperidol with a radioactive tag and monitoring their biological behavior through gamma imaging. The successful development of the imaging techniques and radionuclides under study will permit simultaneous monitoring of the functional status of localized neurons during behavioral testing and the dynamics of drug intake and disposition. Eventually, these compounds may be used clinically to understand the etiology of various neurologic and psychiatric diseases by non-invasive means.

While some investigators are involved with understanding and improving upon current therapeutic regimens for Parkinson's disease, other scientists are seeking to explore the neurochemical, histological, and anatomical systems of the brain which are most affected by Parkinson's disease and related basal ganglia disorders.

The work of an M.D., Ph.D. at the University of Michigan may provide a better clinical understanding of the spasticity associated with Parkinsonism as well as giving insight into the fundamental mechanisms underlying basic spinal cord neuropharmacology. Her experiments will measure neurochemical changes and synaptic function within the spinal cords of rats and cats with spinal cord transections as the animals develop generalized spasticity. In particular, the following measurements will be taken: 1) endogenous levels of GABA, glycine, norepinephrine, and serotonin; 2) inactivation of these transmitters by high affinity re-uptake systems; and 3) changes in synaptic receptors for these transmitters during the development of spasticity after spinal cord transection.

Another investigator who is looking at the recovery of behavioral functioning after CNS injury is at the Philadelphia College of Osteopathic Medicine. Rats are given bilateral hypothalamic lesions. Investigators then explore how several mechanisms — collateral sprouting, neurochemical adjustments, or vicarious functioning, among others — contribute to the recovery of feeding and other behaviors.

Neurotransmitter function in the globus pallidus of monkeys is the target of investigation for scientists at the University of Texas. The effects of acetylcholine (weak to moderate excitant), dopamine (weak excitant), serotonin and substance P (little or no effect), gamma-aminobutryic acid (strong inhibitor), taurine, glycine, and beta-alanine (inhibitors) on the responsiveness of neurons in the globus pallidus are being measured to determine normative functioning in an area of the brain damaged by a number of extrapyramidal disorders.

At the University of Southern California, Los Angeles, an investigator proposes to examine neurochemical relationships involving the nucleus accumbens, looking at this structure during spontaneous locomotor activity and under drug stimulation. A great variety of drugs will be used to characterize the role of the nucleus accumbens. Scientist at Baylor College will also be studying the effects of drugs on the nucleus accumbens of squirrel monkeys during motor activity.

Scientists at the VA Lakeside Hospital have made an animal model of Parkinson's disease by lesioning the nigrostriatal pathway in cats and are studying neurotransmitter balance in the caudate nucleus of the lesioned animal. Their theory is that Parkinson's disease results from an imbalance among the cholinergic, dopaminergic, gabanergic, and serotoninergic systems ennervating this area.

The substantia nigra is the object of study for another investigator at the University of California in Los Angeles. This scientist has made real progress in determining the cytoarchitecture, projection patterns, and functional significance of acetylcholinesterase (AChE) containing neurons in the subtantia nigra. Evidence has been presented that AChE is contained within the dopamine neurons in the pars compacta of the substantia nigra, possibly to inactivate acetylcholine released from cholinergic afferents to the nigra. The investigator seeks to discover if some cells contain both AChE and dopamine and if these cells differ morphologically from those that carry AChE but not DA. Understanding cholinergic-monoaminergic interactions in the nigra may improve our comprehension of the role of the substantia nigra in Parkinson's and Huntington's disease.

One of the mysteries of Parkinsonism is why it occurs so late in life. How long has insidious damage been going on before clinical symptoms appear? We know from disorders such as Tay Sachs, in which pathological changes occur in the brain of the developing fetus although the infant can appear normal until 6 months of age or older, that the compensatory powers of the brain are formidable. Perhaps some underlying process has been going on since youth in Parkinson's disease patients or some traumatic event occurs early in life which leaves the patient asymptomatic but depleted of dopamine and without compensatory powers later in life when an additional neurological assault might trigger the illness. The "safety reserve" of dopamine may be destroyed "invisibly" much prior to the onset of symptoms.

A scientist at the University of Texas is attempting to develop an animal model of such a process. Using microinjections of hydroxydopamine (6-OHDA), a potent neurotoxin capable of selectively destroying catecholaminergic pathways and receptors, he will give young adult rats differing dosages intraventricularly or locally in the region of ascending nigrostriatal dopaminergic systems to produce varying degrees of brain damage. Using analyses of postural and motor abnormalities, he will rate the extent of the behavioral deficit and correlate it with the extent of the lesions. More importantly, he will test the hypothesis that damage in early life can produce symptoms of catecholamine deficiency in later life. In addition, promising methods to reverse these symptoms, such as special dietary regimens, will be studied.

Neurophysiology and Neuroanatomy

Chemical lesioning gives much information about the "wiring diagram" of the basal ganglia, but electrophysiological and anatomical techniques are equally valuable. Scientists at the University of Washington are examining the neurons of the entopeduncular nucleus (ENT) and describing efferents to and afferents from this area, as well as the synaptic actions of ENT cells of several brainstem sites which may link the ENT to the globus pallidus. The investigators seek to clarify what drives the high tonic firing rate characteristic of pallidal and nigral basal ganglia output neurons in awake animals.

At the University of Arkansas, investigators are also using neuorphysiological and anatomical techniques to analyze the organization and function of the motor systems in the cat. The aim of this research is to determine the intrinsic synaptic organization of the neurological substrates involved in preparation for movement. In previous years the investigator has established that the "motor" cortex in the cat sends a somewhat topographical projection into the caudate nucleus. Current research is focused on the relationship of the basal ganglia, including substantia nigra and motor cortex to the mesencephalic locomotor region.

An investigator at the Johns Hopkins University is utilizing electrophysiological and anatomical methodology to explore the motor functions of the basal ganglia. In normal and lesioned monkeys, he is seeking to clarify further the normal functions of the basal ganglia in the regulation of movement and posture and to unravel the pathophysiologic mechanisms underlying movement disorders in man. Trained monkeys are given a visuomotor tracking task while neurons in key brain areas are monitored as the monkeys perform a limb movement. Cells will also be recorded during passive limb manipulations and trained hand and eye movements. The underlying pattern of muscular activity during abnormal movements in primate models is also under investigation. This work comprises some of the best and most exciting single unit analyses of basal ganglia activity in awake monkeys done by an expert in the field.

Understanding the neurophysiological bases for normal and abnormal movements is as important as elucidating the pharmacological mechanisms involved in the production of movement. At the University of Tennessee, a scientist is examining the degree to which mechanical (inertia, elasticity, friction) and neural feedback (reflex) properties of the intact skeletal motor system of man account for voluntary and involuntary motion.

Much of the basic research relevant to the understanding of Parkinson's disease and related disorders focuses on the general study of neurotransmission. At the University of California in San Francisco, scientists are investigating the nature of the long-lasting modulatory changes in the responses of postsynaptic neurons of mammalian sympathetic ganglia produced by dopamine either applied exogenously or synaptically released in the ganglia. This change consists of a long-lasting enhancement of the slow-EPSP (or muscarinic depolarizing response to ACh). Unlike the typical rapid, single synapse-receptor model, this newly described heterosynaptic interaction, lasting several hours, represents a model of the production and storage of a memory trace. The investigators are in the process of characterizing the physiological parameters of the modulatory action of dopamine and unraveling the cellular nature of such charges.

Huntington's Disease

Hungtington's disease (HD), a fatal degenerative hereditary condition, is a disorder of the basal ganglia closely related to Parkinson's disease. While Parkinsonism produces tremor and rigidity, Huntington's disease causes uncontrollable chorea, and gradual loss of the capacity to walk, talk, swallow, and maintain oneself independently. The majority of patients show some degree of dementia, beginning with loss of short-term memory and organizational skills and progressing to a severe incapacity toward the end of the illness. Profound emotional disturbances mimicking schizophrenia and manic depressive disorders may also occur. Huntington's disease is transmitted as an autosomal dominant gene and usually manifests itself between the ages of 35 and 45 years. Children comprise 10% of cases. Treatment is merely palliative and most often entails the administration of dopamine blockers or antagonists. There is no test to determine if a child of a Huntington's disease patient is carrying the lethal gene before symptoms of the illness appear. Patients generally live 10 to 20 years following symptom onset. Biochemically, the disease is characterized by reduced stores of GABA, glutamic acid decarboxylase (GAD), acetycholine (ACh), substance P, angiotensin II converting enzyme and a variety of other neurotransmitters and neuromodulators. There is almost total loss of the small neurons of the caudate nucleus and putamen as well as cortical atrophy, giving rise to a typical picture of enlarged ventricles and sulci on CAT scans.

Genetic Studies

A number of investigators are attempting to identify the abnormal gene that is responsible for the host of physical and mental symptomatology that characterizes Huntington's disease. Based on the genetic prediction that a mutant protein would produce an abnormal charge or weight compared to its homologous gene, and that this difference could be detected through the use of 2-dimensional gel electrophoresis, a scientist at the City of Hope National Medical Center in Durate, California, has been screening over 2,000 gels from multiple brain areas, fibroblasts, red blood cells, and other non-neural tissues. An abnormal double major spot with two satellite spots was finally located in a perchloric acid extract of the putamen and caudate of an HD patient. A similar mutant protein was found in the brains of some patients with classical schizophrenia and manic depressive disorder but not with other neurological diseases. Controls did not have this protein, nor did all HD patients. The investigator has hypothesized that HD and schizophrenia may be allelic variations of the same gene. The spot is not consistently associated with Huntington's disease but does appear in much higher frequencies in the brain of depressives. Work is now being carried out to isolate and characterize these mutant proteins and test for their presence in a larger sample of patients and controls.

Another way to locate the HD gene is to search for a marker in close proximity to it on the chromosome. Investigators at the University of Rochester are looking for possible linkage or allelism of the genes for plasma cholinesterase (E1 and E2) and Huntington's disease. The study stemmed from a report from Britain that there is an increased incidence of the rare E1 gene and C5+ variant of cholinesterase in HD patients. The association may be due to actual linkage or to a modification of the expression of the gene. This research may offer clues as to future research directions, including early diagnosis and treatment.

The fact that Huntington's disease is a genetic disorder can be used to increase the power of scientific investigations. Different genes or alleles of the same gene giving rise to similar phenotypic expression can still produce biochemical differences. Using tissues from a large pedigree of affected individuals mitigates against genetic heterogeneity which can confuse the interpretation of research findings. The validity of any finding purporting to be an expression of the gene product or closely linked to it can be quickly tested by seeing if the finding segregates with the HD gene in a pedigree. Again, a large pedigree is needed. Investigators also have need for different types of research subjects. In a disorder as relatively uncommon as Huntington's disease, and with family members so widely dispersed geographically, a centrally located data bank of pedigrees is an invaluable aid to research. A contract for a Huntington's Disease Roster was given to the University of Indiana to develop such a roster, in response to a recommendation of the Commision for the Control of Huntington's Disease and Its Consequences. The Roster can match together family members with different names and from disperate states, thus creating much larger pedigrees . It can also select specific families needed for particular research projects and serve as an intermediary between the scientist and the subject.

Studies of Non-neural Tissues

For many years, Huntington's disease has been considered strictly a brain disorder. In recent times, however, scientists have questioned whether the HD gene might produce modifications of non-neural tissue. Since the nucleus of every cell contains the HD gene, perhaps subtle expressions of the gene make minor but detectable alterations in the cell. Or perhaps a normally quiescent gene can be induced to "turn on" in culture to reveal its aberrancy in the laboratory. Scientists from the University of Kentucky have been taking the lead in demonstrating that the HD gene may well cause a generalized membrane defect. Subjecting erythrocyte ghosts to analysis by electron spin resonance (ESR), scientists have discovered an alteration in the physical state of membrane proteins in HD patients, as compared to normals and other neurologic disease controls. Red blood cells from HD patients also showed an increased tendency to form stomatocytes, suggestive of increased membrane rigidity. Increased NA+, K+-APTase, and sialic acid was also noted in the HD erythrocyte membranes. A thorough investigation of these findings using ESR, gas-chromotography mass spectrometry, scanning electronmicros- copy and enzymatic analyses is now in progress.

Other indications that HD might involve a generalized membrane defect have come from studies of skin fibroblasts. Investigators at the University of Oklahoma are exploring biochemical alterations in fibroblasts from HD patients. GAD activity and GABA pool size is abnormal in HD fibroblasts. Additionally, glutamate has been found to be selectively toxic to HD fibroblasts compared to normals and other disease controls. Using fibroblasts may provide a "window "on brain functioning and permit a variety of studies not ethically possible now. The toxicity finding, if validated, could provide a useful marker for the HD gene in culture.

Another investigator at Duke University is pursuing his preliminary data which indicate alterations in cell attachment and protein glycosylation in HD fibroblasts. In particular, glutamine was found to be toxic to HD fibroblasts leading to changes in morphology and eventual cell death; these effects are partially reversed by glucosamine. On the basis of these and other observed abnormalities, the investigator suggests that HD fibroblasts express a membrane defect due to abnormal glycosylation of proteins and that this impaired glycoprotein synthesis may be correctable by a diffusible factor in serum. His work proposes to characterize these differences further, and to pursue the hypothesis that the enzyme responsible for glucosoamine synthesis, fructose-6-phospate glutamine transaminase, is the defective metabolic step in producing the disease.

At the University of Washington, in Seattle, investigators are studying plasma membranes isolated from skin fibroblasts in an attempt to correlate changes of fluidity and structural modifications in the membrane with the age of the donor and with the aging of cells in culture. The actions of flourescent probes in isolated plasma membranes will be examined together with an analysis of membrane lipid protein composition in order to develope a model of the fibroblast plasma membrane. This project will hopefully demonstrate if there are changes in membrane fluidity and composition which correlate with cell aging or with the presence of a disorder such as Huntington's disease.

Ever since the revolutionary work of Gajdusek and Gibbs stimulated scientists to consider more unconventional etiologies for chronic degenerative neurological disease, the role of virology and immunology in neurologic disease has received increased attention. It is conceivable that a virus could become integrated into the genome to produce the symptoms and Mendelian inheritance pattern of Huntington's disease. A scientist at the University of California is attempting to explore this hypothesis. His current work is aimed at characterizing a cellular immune response in HD patients which was discovered in his laboratory. Using the mixed lymphocytyes inhibition assay (MLF), this scientist discovered that lymphocytes from HD patients appear to be immunologically sensitized to HD brain tissue, but not to brain tissue from normals or other patients. This finding may be due to the leakage of antigens through the blood brain barrier due to brain deterioration or to the presence of a possible specific HD brain antigen.

Biochemical and Structural Studies

Animal models have always been important in the understanding of the etiology, pathogenesis, and possible treatment of disease. HD is no exception. Recently, a new animal model was created by the injection of kainic acid, a highly toxic glutamate analogue derived from seaweed, into the striatum of rats. The kainic acid produces a selective degeneration of striatal intrinsic neurons, and neurochemical and histologic alterations in the nigro-striatal circuit that closely mimic those found in HD. Fibers of passage are less affected by the kainate, and the chemical has no effect if cortical-striatal glutamatergic pathways are severed.

An investigator at The Johns Hopkins University School of Medicine is continuing his work elaborating of the lesioning effects of kainic acid. In vitro measurements will be made of the specificity of receptor binding of kainic acid and kainic acid-induced release of labeled neurotransmitters from prelabled slices of hippocampus, striatum, and cerebellum. In vivo studies will focus on the effects of kainic acid injections on local brain energy metabolism. An important element of the in vivo experiments will be efforts to "rescue" vulnerable tissue through pretreatment with a variety of anesthetic and anti-convulsant drugs. This research may some day lead to prophylactic treatments for patients and individuals at risk for Huntington's disease.

In addition to kainic acid, ibotenic acid and glutamic acid have excitotoxic effects. An investigator at the University of Tennessee proposes to study the effects of lesions and drugs on the neurotoxicity of these three amino acids, focusing on the rat hippocampus. Drugs to be used include morphine, naloxone, diazepam, gamma-Aminoadipic acid, and amino acid esters. Lessons from the in vivo experiments will then be translated to an organotypic culture of rat hippocampus. Using ultrastructural techniques, the role of the dendritic spines in the initiation and propogation of the degenerative process will be carefully explored. Understanding the mechanisms by which excitotoxic amino acid kill cells may lead to insights on the neurodegenerative disorders like Huntington's disease which are characterized by cell death.

The discovery that GABA and its synthetic enzyme GAD were reduced in the brains of HD patients led to a number of different research questions. Scientists at Harvard Medical School are exploring the neuropharmacology of GABA function through the study of specific enzymes importantly involved in GABA metabolism. Investigators have developed highly potent and specific irreversible inactivators of GABA-transaminase (involved in degradation) and GAD (involved in synthesis). Scientists can thus regulate levels of GABA in tissue culture and in vivo. Using mice and chick embryos and tissue cultures, investigators will create models of HD and other disorders involving GABA metabolism, such as epilepsy. These models can be used to test potentially new treatments that would raise GABA levels. In tissue culture, the role of these two enzymes in the formation of GABAergic synapses and neuronal development can be studied in great detail. The investigators also propose to develop a new mapping technique for GABAergic neurons in culture and in vivo using radiolabled decarboxylase inhibitors coupled with autoradiography.

The cytoarchitecture of the neostriatum is one of the most complex in the brain. While we know which neural structures project to the neostriatum and which striatal neurons have local circuit connections, little is known concerning which types of neurons receive what synaptic inputs or whether there is a systematic distribution of synaptic boutons within the striatum. A scientist at the Uniformed Services University is using both light and electron microscopic techniques to examine the various types of neostriatal neurons and analyze the distribution of different synaptic terminals on the dendrites and somata of these cells. Using both Golgi and EM-autoradiography, he will study different types of neostriatal neurons and the afferent projections to them in the same specimen. Synaptic terminals from local circuit axons and axon collaterals will also be identified at the ultrastructural level. This meticulous work will gradually build a detailed picture of the organization of the adult mammalian neostriatum and provide an anatomical background for future structural and biochemical studies.

Scientists at the University of Indiana will also be doing mapping experiments to determine the regional distribution of cholinergic, GABAergic and glutamatergic pathways within the striatum. Interrelationships among these neuronal systems in the rat striatum will be examined.

Interdisciplinary Workshops

A crucial need in Huntington's disease research is to recruit new investigators to the study of this relatively little known disorder, and to generate new research hypotheses. The Hereditary Disease Foundation has had a ten year program of sponsoring interdisciplinary workshops on Huntington's disease and other degenerative disorders to achieve these ends. Participants range from postdoctoral and medical students to department chairmen and span a wide variety of scientific expertise in basic and clinical areas. Four workshops a year are being supported through a grant to the Foundation.

Huntington's Disease Centers

One of the most exciting initiatives in Huntington's disease research was the award of two grants in FY80 to establish "Centers Without Walls", as recommended by the Congressionally mandated Commission for the Control of Huntington's Disease and Its Consequences. Each Center supports clincial and basic research aimed at uncovering the etiology and pathogenesis of Huntington's disease and developing new physiological and sociopsychological treatments for the disorder. One Center is located at The Johns Hopkins University and is composed of a number of different departments within the Medical School, such as psychiatry, neurology, genetics, and the School of Public Health. The program consists of nine clinical and basic research projects. Clinical studies range from case-finding and epidemiological studies, and research on genetic counseling, to the exploration of eye movements as clues to early disease process and diagnosis, and the amelioration of swallowing difficulties. Basic science projects include the localization and measurement of neurotransmitters, neuropeptides, and enzymes in the brain, and the detailed elaboration of the structure and function of the basal ganglia, an area of the brain affected by Huntington's disease, Parkinson's disease, Tourette's syndrome and many other movement disorders. Investigators are in the process of locating all patients and families in Maryland and surrounding states. The J. Earle Moore Medical Genetics Clinic at The Johns Hopkins is providing the clinical "hub" of the "Center".

The other "Center" represents a consortium of departments within different institutions, including Massachusetts General Hospital, McLean Hospital, Boston University, Tufts New England Medical School, the Boston Veterans Administration Hospital, and the University of Massachusetts, and supports 10 scientific investigations in participating institutions. Patients and their families are being seen at clinics in the different Centers. A number of the projects focus on mapping and measuring levels of neuroendocrines and neuropeptides. These investigators are developing new procedures for analyzing brain tissues which will be of value for looking at all brain disorders. In addition, they are examining tissues from patients dying of other devastating brain diseases such as schizophrenia, Alzheimer's disease, Parkinson's disease and others. A team of molecular geneticists at Massachusetts General Hospital is using recombinant DNA techniques to try to determine the exact chromosomal location of the abnormal Huntington's disease gene. These scientists are in the process of mapping the human genome, uncovering "markers" on chromosomes which will greatly advance the localization of other genetic diseases. They use tissue samples from families with special pedigrees, particularly from Venezuela.

Venezuela Project

A major project of the NDP Huntington's Disease Program has been a collaborative study in Venezuela on a unique population of Huntington's disease families living on the shores of Lake Maracaibo. The HD focus was established in 1860 by a gene carrying Spanish sailor and has grown to encompass more than 200 patients and 2,000 relatives. In July, 1980, a contract was signed with the University of Zulia, in Maracaibo, to enable a team of Venezuelan and U.S. scientists to study the families neurologically, genetically, psychologically and sociologically. The Venezuelan focus is particularly valuable for research purposes for the following reasons: 1) a single founder means that all patients have inherited an identical HD gene. Genetical heterogeneity which may occur if the gene has different sources of origin can confuse the interpretation of research findings. 2) Families are extremely large with many members both affected and unaffected. This type of family structure is ideal for genetic linkage studies. 3) The families are interrelated with a relatively high frequency of two people "at risk" for the disorder marrying and producing children who have a higher probability of being homozygotic, if a "double dose" of the gene is not lethal in utero. The biochemical defect may be more obvious in a homozygote. 4) None of the patients are taking any medications so that drug effects do not confound the data.

In March, 1981, the first phase of the study took place. An interdisciplinary team spent three weeks in Venezuela and took blood and skin samples from 112 individuals: patients, family members and controls. Fifty-five patients were examined neurologically on film and 20 patients were give psychological tests and medical and social history questionnaires. Geneticists from the Boston "Center Without Walls" will be analyzing the tissue collected using recombinant DNA techniques to identify DNA polymorphisms linked to the HD gene. Transformed lymphocyte lines and fibroblasts are available for any qualified investigator to use and may be obtained from the Institute of Medical Research, Camden, New Jersey. The Venezuelan pedigrees have been computerized and are part of the Huntington's Disease Roster at the University of Indiana. A return trip is anticipated for FY 1982.

Alzheimer's Disease and Other Dementias of Aging

There was a time when the frailities and foibles of age were thought to be the almost inevitable price for longevity. With the impressive growth of neurobiological research, however, we are rethinking our future as well as uncovering the present. The devastating intellectual and physical decline, which is the hallmark of senile dementia, is seen now as a disease of aging; a pathological deviation from the normal developmental process. Clinical syndromes have been described, structural abnormalities identified, and cellular anomalies uncovered.

The problem of the dementias in the United States has assumed alarming proportions. Statistics from the National Center for Health Statistics indicate that about 12% of our population is 65 years or older. Based on northern European estimates of prevalence and incidence of dementia, there are approximately 1 million severely demented and another 3 million moderately to mildly demented persons in the U.S. today. The life expectancy of the severely demented is only one-third to one-half that of their age-matched controls.

At least two-thirds of elderly people with severe dementia suffer from Alzheimer's disease. In recent years, many scientists have argued that distinctions between pre senile dementia and Alzheimer's disease are arbitrary and meaningless. Although senile dementia of the Alzheimer's type (SDAT) and classic Alzheimer's disease, which usually affects people under the age of 65, may well be the same disorder, other forms of senile dementia with differing etiologies give rise to similar symptoms. Intellect fails dramatically, hallucinaions and delusions may occur, aphasia, disturbances of eating and sleeping, cachexia, and total disbility to care for oneself.

The spongiform encephalopathies, kuru and Creutzfeldt-Jacob disease (CJ), may also produce diseases considered presenile dementias. They are the consequence of an unusual virus, or "viroid", which has properties unlike most conventional viruses. The span between infection and signs of the illness can be quite short, such as several months or a year as with CJ, or as long as 8 or 10 years. Once apparent, these "slow virus" diseases are characterized by vacuolation and neuronal death, astrocytic proliferation and hypertrophy, axonal and dendritic degeneration in Purkinje cells, and presence of amyloid plaques, but no evidence of infection.

Occlusions of cerebral blood flow, known as multi-infarct dementia, also give rise to a clinical picture similar to that of SDAT. Sophisticated imaging devices, such as the CAT scan, help in making differential diagnoses.

The dementia associated with Parkinson's disease has received little attention, but it is a clinical entitity of significance. Since the advent of L-dopa, improved motor control and prolonged life span has made the cognitive changes in this disorder more obvious. Parkinsonian dementia may be much more widespread than the special focus of patients on Guam who suffer from amyotrophic lateral sclerosis and Parkinsonian dementia. These patients, as well as other "usual" Parkinson's disease patients, show the neurofibrillary tangles so characteristic of Alzheimer's disease. The significance of the number and distribution of these tangles is being explored.

Structural Studies

The majority of the research supported is aimed at clarifying the structural and biochemical abnormalities which characterize Alzheimer's disease. A number of studies focus on cytoskeletal changes, the neurofibrillary tangles and senile plaques, which are the hallmark of Alzheimer's disease. These tangles appear in the neuronal soma as aggregates of paired helical filaments approximately 200 A in cross section, with a twist approximately 80 A along their length. Both neurofibrillary tangles and their normal, unpaired, and nonhelical neurofilamentary counterparts have been identified as proteins with a molecular weight of around 50,000 daltons.

Investigators at Albert Einstein College of Medicine have had a long standing interest in elucidating the structural abnormalities and changes found in Alzheimer's disease brain tissue. Surprisingly, meticulous cell counts conducted there indicate that there is no major decrement of cortical neurons relative to age-matched controls. The acetylcholine muscarinic receptors of the cortex are maintained even though there may be a 75% to 95% loss of cortical choline acetyltransferase (ChAT). Localization of this synthetic enzyme and its receptor is being pursued in human and animal brain tissue by enzyme immunohistochemistry and radiography. Microscopic, histologic and biochemical techniques will be used to compare young and old brains and normal and senile dementia of the Alzheimer's disease type brains.

In other studies, experimentally induced lipofuscin and aluminum induced tangles will be investigated as well as axoplasmic flow in aging animals. Investigators are isolating and characterizing intraneural paired helical filaments, mapping their peptides, binding properties, and antigenic determinants. The biophysical properties of human and porcine neurotubule assembly and disassembly are being explored. Using proteins isolated from the autopsied brains of patients dying with Alzheimer's disease, both young and old, and Guam Parkinsonian dementia, the mechanisms of action of colchicine and vinblastine and the regulatory role of Ca, Mg, and Zn ions on microtubule assembly will be explored.

Understanding of the biology, chemistry and pathology of the fibrous proteins of the nervous system in health and in disease states has been the objective of many NINCDS supported researchers. Several different laboratories are investigating paired helical filaments in the presenile and senile dementias as well as in Down's syndrome. Twisted tubules have been partially purified by investigators at New York University Medical Center. The relationships among various neurofilaments and between these filaments and tubulin is being explored. Another investigator at Boston Biomedical Research Institute is characterizing the chemistry and function of neurofilament proteins with regard to their sequencing, immunoreactivity, comparability with other glial fibrillary proteins, and tendency to proliferate in neurons treated by neurolathyrogens.

The role of the microtubules in maintaining cell integrity and function is exceedingly complex; explaining it may be necessary for understanding normative behavior as well as a variety of different disorders, including cancer and the dementias. In Colorado, investigators are looking at clonal cells of the mouse neuroblastoma C1300 that possess high concentrations of tubulin and whose content of microtubule can be directly regulated by growth conditions. The role of microtubule associated proteins in differentiation will be explored as well as the possibility that these accessory proteins regulate where and when tubulin polymerization occurs within the cell. Work is also continuing on localizing and characterizing GTP binding sites in brain tubulin using photo-affinity labeling reagents.

Just as the structures within the cell have sparked interest, the structure which encloses the cell, that elaborate and vital membrane, has attracted the attention of others. Investigators at the University of South Carolina are asking if membrane transport alters with age. As the cell ages, can it still acquire from the extracellular fluids across its membrane the necessary metabolic substrates for energy metabolism and protein synthesis? Do membrane functions in neurotransmission remain the same?

The biophysical characteristics of membrane aging is also the object of study of investigators at the University of Southern Alabama. Using electron spin resonance techniques, the relationship of monoaminergic systems to cellular changes due to aging will be explored. Two forms of monoamine oxidase with quite distinctive properties, MAO-A and MAO-B, have been identified. These enzymes have been shown to increase markedly in activity in specific regions of aging brains. A study of the MAO-membrane system should contribute to our understanding of the aging process in biological membranes.

Biochemical Studies

Other research sponsored by the Institute is aimed at characterizing the biochemical alterations in SDAT. A key feature in these changes are the neuritic or senile plaques, dense masses of extracellular amyloid surrounded by enlarged neurites, mostly axonal boutons containing degenerating mitochondria and lamellar lysosomes.

The complex interaction of the endocrine system with neurotransmitters and neuromodulators is an area recently coming to the forefront of scientific attention. At the University of Pennsylvania, scientists are looking at the role of neuroendocrine factors in regulating catecholaminergic receptors in the central nervous system. They are seeking to determine if the reduced ability of brain tissue to regulate the density of these receptors may impair neuroendocrine feedback mechanisms. Age related changes may effect the density, function, and adaptive capacity of the cholinergic receptors in the central nervous system. Thus, age may work its effects on neurotransmitters through the mediation of the neuroendocrine system. Through *in vitro* culture studies using the pineal gland from young and old rats, investigators are examining the rate of catecholamine receptor synthesis and turnover, and in particular, how these processes are affected by age.

The role of the immune system is now being taken into account in studies pursuing the etiology of neurological disorders. Investigators at Sloan-Kettering Institute for Cancer Research have had a long history of looking at the interface between autoimmunity, immunodeficiency, and central nervous system disorders. Recent data indicate that patients who are IgA deficient absorb foreign proteins through their intestines thus leading to the development of circulating immune complexes. These findings further explain the link between the development of autoimmunity and immunodeficiency in patients. In addition to looking at the effects of dietary intake on autoimmune disease and atherosclerotic cardiovascular disease, investigators are attempting to elucidate immunologic mechanisms in chronic degenerative CNS disorders, such as Alzheimer's disease. Dietary manipulations will be studied and comprehensive immunologic analyses and lymphocyte characterizations will be made on patients with Down's syndrome and senile dementia.

Animal Models

Animal models of dementia are hard to come by since dementia involves the loss of a capacity we cannot be sure animals ever had. Nonetheless, scientists at the City of Hope in Duarte, California, are studying Drosophila mutants which exhibit both genetically programmed movement disorders and shortened life. They are trying to determine if the shortened life span is also under genetic control, and if so, how the genes produce their effect. Recent data suggest that the thorax of Drosophila may act as an aging center. An intriguing new finding by this laboratory is the isolation of a long-lived mutant. Dubbed "inactive" by its discoverers, the creature can walk, fly, court and mate but prefers to sit around and do nothing. This fly bears witness to the adage that "burning the candle at both ends" is deleterious to one's health. Since this laboratory is one of the most pioneering and dedicated, one hopes that they will soon discover a long-lived mutant in the Picasso-Casals mode.

At the University of Pennsylvania, an investigator is looking at the aging process in cultured neurons. In the process, he is developing culturing techniques for neurons which may benefit research on many different brain disorders.

Mutant mice can be excellent systems for studying degenerative processes. An investigator at Indiana University is studying the Purkinje cell degeneration (PCD) mutant as a model of selective cell loss in the nervous system. One model of both normal and pathological aging holds that there is genetically programmed cell death which gives rise to the characteristic signs of aging. In the PCD mutant, all Purkinje cells irreversibly degenerate. Preliminary work by the investigator on tissue culture explants of PCD cerebellum indicate that degeneration occurs at post natal day 17. The selective degeneration of a particular cell type allows the researcher to look at neurotransmitter functioning in the cerebellum, focusing on GABA which is a primary neuro- transmitter for Purkinje, Basket, and Golgi cells.

The assumption that aging entails cell loss can be meticulously tested as new technologies permit computer assisted graphs and reconstruction methods to enumerate and characterize the nervous system. When specific brain areas have been carefully assessed, several studies have indicated little or no cell loss. But the common wisdom about aging is that it entails programmed cell death in the same fashion that early development requires cell death. New technology permits the generation and analysis of quantitative data concerning neuron types and numbers, and measurements of axons and synaptic distributions. An investigator at Children's Hospital Medical Center, Boston, is looking at four separate neuronal systems to test the hypothesis that neuronal death is a feature of aging, and that its rate depends on changes in synaptic connections of the neurons at risk. The systems of interest are: a) the visual system, b) sciatic nerve, c) cerebellar cortex, particularly Purkinje cell neurons which are known to decrease in number with age, and d) cerebellar nuclei, particularly synaptic connections in aging normal mice and mutant mice which loose portions of their axonal input.

Clinical Studies

A large program project on "Senile Dementia: Alzheimer and Vascular Disorders" at Albert Einstein College of Medicine takes an interdisciplinary approach to studying the dementias. Clinicians, biochemists, neuropathologists and neurophysiologists, psychologists, mathematicians and many others turn their talents toward discovering the origin of these diseases and developing appropriate treatments. Investigators are interested in the nature, incidence, prevalence and course of senile dementias. The identification of risk factors and prevention will receive considerable attention.

The program has three major sections. Section I consists of laboratory studies relating to the etiology and pathogenesis of senile dementia, particularly of the Alzheimer type (SDAT). One project will attempt to grow paired helical filaments in culture. Another explores the possibility that a persistant virus infection may cause SDAT. Two other projects will focus on the localization (through immunocytochemistry) and regional distribution of five peptides in normal and senile human brains and explore the possible relationships of these peptides to the composition of neuritic plaques and tangles.

Section II continues several clinical and psychological studies of SDAT now in progress. A longitudinal study of 500 residents of a nursing home has generated a wealth of biological and psychological data. As residents die, approximately 40 brains a year will be available for correlations of postmortem biochemistry with premortem clinical parameters.

The third section consists of a large prospective study of about 640 people drawn from two nursing facilities and "normal" elderly volunteers drawn from the community. The prospective study will identify risk factors in dementia produced primarily by multiple cerebrovascular infarcts.

The diagnosis of Alzheimer's disease is made on clinical grounds, more as a result of the elimination of other disorders than from specific signs of the illness itself. Confirmation must await autopsy. At the University of California at Irvine, an investigator is in the process of developing a rapid neuropsychological screening test which, hopefully, will be able to serve as an early screen for dementia. Development of the test will take place in a large, well-defined retirement community in Southern California. Laboratory findings and other data will also will also be collected on this sample, making it an excellent prospective study of a very different sample than the Einstein study for the identification of risk factors and possible etiologic clues.

New Directions

The NINCDS is actively seeking to increase the level of research effort directed at Alzheimer's disease and other diseases of aging. In concert with the National Institute of Aging, a Program Announcement has just been released soliciting grant applications on research into the etiology, pathogenesis, treatment and prevention of these devastating disorders.

Tardive Dyskinesia

A disorder closely related to Huntington's disease in symptomatology appearing as a result of prolonged neuroleptic treatment is tardive dyskinesia. Unfortunately, no effective treatments have been developed for this disorder as well, but scientists at the Portland, Oregon, Veterans Administration Hospital are trying to determine a subgroup of this population which is responsive to the therapy by deanol, a possible acetylcholine precursor.

At nearby University of Oregon, another scientist is exploring the role of GABA in the production of tardive dyskinesia. The effects of diproplyacetic acid (DPA) are being tested on patients with tardive dyskinesia in a double-blind study, while guinea pigs provide a model for the study of DPA effects on behavior, brain GABA and dopamine receptors.

General Studies

The major role of genetics in determining susceptibility to disease, phenotypic expression of illness, response to drug treatment, and a host of other factors is gradually unfolding. One of the pioneers in the study of inherited variations in human neural proteins is at Yale University. She is developing a general methodological approach through the specific study of the structural basis of inherited differences in functional capacity of three proteins critical to nerve function: monoamine oxidase, catechol-o-methytransferase, and the beta subunit of nerve growth factor. Proteins from peripheral tissue will be analyzed, including placenta, platelets, lymphocytes and cultured skin fibroblasts. The investigator has already discovered that the structural gene for beta-nerve growth factor is altered in familial dysautonomia. This finding may lead to rapid strides in the treatment and prevention of this disease. In similar fashion, the study promises to yield important data on protein polymorphisms in human populations.

The biochemical, structural, functional characterization of the basal ganglia without reference to any specific disorder, has been drawing the attention of an increasing number of scientists. At the University of Texas, investigators are trying to understand the GABA receptor in all its complexity. The effects of drugs such as anionic transport inhibitors, anticonvulsants, and psychoactive agents are being explored as well as the possibility that altered chloride permeability may be a factor in disorders involving altered GABAergic function.

At the University of Maryland, investigators are looking at the potential precursors of gama amino butyric acid to explore alternate pathways for GABA production in the brain. The pharmacological properties of intrinsic caudate neurons in cats are under investigation at the University of South Carolina.

Investigators at the University of Minnesota are turning their investigation to a detailed look at cerebellar anatomy and physiology. Their research program is directed towards an analysis of the effects of proprioceptive and exteroceptive inputs on spinocerebellar systems and on specific regions of cerebellar cortex.

The biochemical response to a structural change in a genetic mutant involving the loss of one particular cell type will be studied at Tuft's University. Purkinje cell degeneration mutant mice (PCD) will be compared with granule cell deficient mutants to learn the effects of Purkinje terminal degeneration on target cells in the deep nuclei. If a dense GABA releasing afferent pathway is severed, what is the response of the deep nuclei?

Questions of brain asymmetry in response to cerebral damage are being explored by investigators at Mt. Sinai School of Medicine. The neuroanatomical structures involved in producing and maintaining laterality, including the role of the commissural pathways are being identified while investigators also look for neurochemical asymmetries in different brain regions. Rats which demonstrate lateral turning reactions with chemical lesions will be studied to learn further about this rotational response and its relationship to cerebral asymmetry. Differences between spontaneously rotating and non-rotating rats will be identified. At the same institution, another investigator is conducting a related study analyzing the functional relationships between the substantia nigra and the striatum.

A study at State University of New York at (SUNY) - Stony Brook looks at the trigeminal input to the basal ganglia, in particular, the globus pallidus and entopenduncular nucleus. Electrophysiological techniques will be used to examine the effects of the basal ganglia on the organization of oral facial behavior.

While investigators at SUNY are looking at the input of one neuronal system on another, investigators at the University of California at Irvine are looking at axonal collateralization from monoamine nerve cells in the CNS. The investigator plans to determine the percent of individual cells within a given nucleus of interest that send axons to different regions of the brain and the percent of cells sending them to the same set of regions. Three particular regions will be examined for their axonal growth into the same or other cortical, limbic, or striatal structures. A projection log of key areas of collateralization of monoaminergic neurons will be the result of this research. A unique feature of the work is the use of double labelling techniques to see if the same neuron projects to two or more different areas of the CNS.

The primary neuronal cell type in the striatum is the striatal spiny efferent neuron (SENS). It receives presumed monosynaptic input from both cortex and thalamus and is reciprocally connected with the substantia nigra. Stimulation of various striatal afferent systems produces different synaptic actions on SENS. An investigator at Michigan State University is attempting to explain these different actions by morphological studies of synaptic inputs which he will correlate with physiological studies of these same afferents to intracellularly labeled striatal spiny neurons.

Future Goals

The wealth of research findings is steadily expanding, but so too are the numbers of victims afflicted by the disorders of aging. Increasing numbers of new investigators must be recruited to this area to maintain and accelerate the momentum of discovery.

OTHER NEUROLOGICAL STUDIES

This section consists of four main categories of research projects:

Neural Aspects of Learning and Behavior
Disorders of Other Senses with Emphasis on Pain Research
Neuroendocrine Studies
Hereditary Lipid Storage Disease and Other Metabolic Disorders

The research activities in these four categories are described in the following reports.

NEURAL ASPECTS OF LEARNING AND BEHAVIOR

In this category there are six projects. These projects are directed towards the identification of anatomic and morphological substrates in the central nervous system that influence behavioral alterations. Investigations are conducted to assess possible behavioral consequences of genetically determined traits as related to structural organizations in several strains of animal models. A question is being tackled of whether, or not, in children, the degree of lateralization of handedness is related to intelligence. Towards this end, the correlation of degree of handedness with learning ability is being investigated. The other aspect of learning and behavioral processes is related to the identification of macromolecules and biochemical markers that may be important in establishing long-term memory. In these studies changes in specific proteins during acquisition of new behavior have been observed. It is hoped that eventually such studies may help explain the mechanisms of learning, memory and behavioral manifestations.

DISORDERS OF OTHER SENSES WITH EMPHASIS ON PAIN RESEARCH

In this category there are 29 projects. About two-thirds of these projects are related to pain and pain mechanisms. A narrative on this subject is also included. Other projects in this area are related to motor control, neural mechanisms subserving position sense, and sensory coding. The emphasis is upon ascending spinal pathways conveying static position signals, the identification of the types of receptors that contribute to these signals and the central representation of these signals within the brainstem, thalamus and sensory cortex. The hypothesis is being tested about the nature of segmental and supraspinal motor control systems and the variables that are controlled bysegmental reflex areas. Studies are also designed to investigate the neural processes underlying the initiation and guidance of voluntary limb movement to answer questions, such as, what parameters of movement are specified by central programs and how are these parameters expressed in the neural activities of the major motor systems. Also, what role does afferent information play in the initiation and control of movement and how can this information be used by the nervous system to alter existing programs to better achieve the behavioral responses. In another study the role of certain reflex systems in the control of functional human behaviors are being investigated. For example, the specific behavior examined is stepping-down; an act necessary for full mobility. Knowledge of the stresses incurred during step-down may offer an important basis for evaluation of the mobility needs of the partially disabled and geriatric populations. More generally, the data may indicate the importance of considering human reflex systems not only when the person is in a passive state, but rather during performance of active behavior because reflex responses are dependent upon the functional state of the organism.

Pain

Introduction

Pain is the ultimate manifestation of some underlying etiological factors. Main causes of Pain can be divided into two categories: one coming from without (heat, electricity, mechanical injuries, etc.) and the other from within (pathological and metabolic). Our primary goal is to alleviate this unpleasant sensation. This goal cannot be achieved realistically until we understand the causes that produce pain. For example, if we can cure arthritis, there is then no pain because this disease exists no more. As such pain is neither a pathological or an environmental entity. Until we progress to that ideal stage, some realistic goals can be established and to achieve these goals, some practical approaches can be developed. The present state-of-the-science takes into account that no matter what underlying cause, plain is a real entity, and as such, needs remedial action.

The field of pain research and theory has developed rapidly in recent years. These developments have come from many disciplines, including psychology, physiology and clinical medicine. As a result of this progress, exciting new techniques have been proposed for the treatment of pain.

The clinical syndromes which result from peripheral nerve injury bewilders the scientist who tries to understand them. Still worse, the failure to solve the problems they present means prolonged suffering and tragedy to many patients. People who face death due to a malignant disease such as cancer also face the prospect of extreme pain. Those who sustain brain damage as a result of a stroke may suffer severe pain for the rest of their lives. Drugs help, up to a point. Surgery offers some slight hope. But the pain may continue unabated until the end. Pain, then, is more than an intriguing puzzle. It is a terrible problem that faces all humanity and urgently demands a solution.

This report highlights the research supported by NINCDS as related to the six goals set by the pain panel of the National Research Strategy for Neurological and Communicative Disorders. Presently this institute is supporting about 21 projects with an investment of about one and a half million dollars.

Identification of Pain Receptors and Characterization of Their Pysiological Properties

Most parts of the body or organs are supplied with one or more types of pain receptors. For example, most areas of skin contain more than one type of nociceptors. One type associated with myelinated fiber, responds to intense mechanical stimulation only. Another type is polymodal, which is associated with an unmyelinated fiber and excited by noxious stimulation such as heat, mechanical injury and chemical stimulation. A third type of nociceptors has been described as being associated with myelinated fibers and these respond to heat and mechanical injury. Both myelinated and unmyelinated receptors are found in muscle. Visceral pain is much less understood than skin and muscle pain. Since the viscera is well protected from the outside, the pain receptors in this region are probably activated by irritants produced by metabolic disturbances. So far, no definite pain receptors have been identified in the digestive tract.

The capacity to distinguish which primary sensory element contributes to a neuron's afferent input is a recent development. It is based on a decade of research establishing receptive characteristics for primary afferent fibers in nerves innervating a given body region. The considerable degree of selectivity in the responsiveness of different receptors and the relation of afferent fiber diameter to receptor type are points allowing the analyses of the projection from given receptor types. Electrophysiological recordings and the effects of lesions have been attributed to give types or classes of neurons on the basis of the source of activity. The recent evolution of an experimental technique allows a direct comparison, in the mammalian nervous system, of such structural features as connectivity for a particular neuron whose functional characteristics need to be established.

The sensitization of the C-fiber polymodal nociceptors can be related both to reactions associated with nociception and to the sensation of pain. For the latter, direct correlations have been made between activity in human C-fiber polymodal nociceptors and the report of pain by human subjects.

The functional significance of the substantia gelatinosa is known to be related to Lissauer's tract, which at various times has been implicated in the intraspinal transmission of impulses related to reactions typical of pain and to the manipulation of sensory information between segments or classes of receptors. It is quite clear from the clinical literature that injuries involving partial denervations or other interference with the afferent input to a spinal segment of the trigeminal input leads to essentially incurable dysesthesia, including various aberrations associated with pain. A great variety of both naturally occuring and artifical substances introduced excite or modify the behavior of these elements. For this reason, the work to date has been focused on attempts to use specific chemical agents to interfere with the evolution of background discharge. Since bradykinin is a prime candidate involved in the inflammatory reaction, as well as having been implicated in the process leading to skin pain, attempts were made to interfere with the bradykinin action by adding carboxypeptidase B to the perfusion fluid. Unfortunately, no definitive results were obtained in these studies. The results with an antiserotonin agent, methysergide, alone or in combination with an antihistamine were more interesting. In particular, it was noted that the use of the antiserotonin agent tended to depress the development of background discharge following repeated heat stimulation. The effects upon the sensitization (enhanced responsiveness) were equivocal. Attempts to deplete serotonin by pretreatment with paracholorophenylalaine yielded results compatible with those obtained with methysergide.

Future trends: Polymodal receptors are prime candidates for forming part of the normal afferent system leading to the sensory experience. Significantly, they are known to be readily excitable by a variety of noxious stimuli, including, injected agents and irritant chemicals. A systematic survey would be made of the behavior of the polymodal nociceptors and other C-fiber receptors. A comparison of the behavior of each element to its own past activity, as well as comparison to other units studied, in the absence of stimulation, would serve as a guide for determining the possible influence of sympathetic stimulation upon this class of nociceptors. The work on the sensitization of nociceptors would be pursued with pharmacological agents or the efferent sympathetic stimulation. Similar work would be undertaken to identify and locate pain receptors in different organs of the body.

Pathways and Structures Modulating Pain

Of the several pathways contributing somatosensory information to rostral centers in man and lower primates, only the projection in the lateral and ventral columns of the spinal white matter has been established as crucial to nociception and pain sensation. In contrast to the paucity of evidence suggesting that dorsally-located tracts are essential for nociception and sensory pain, the evidence is overwhelming that fibers located in the ventrolateral white matter of the spinal cord are crucial to this function in normal individuals. Classically, sensory pain and temperature sense are held to be affected in parallel by lesions of the ventrolateral spinal tracts; however, there appears no doubt that both natural and surgical interruption of parts of this system may cause a dissociation, leaving sensory pain relatively intact while interfering with temperature sensibility, or vise versa.

Regional or segmental modulatory influences on the effectiveness of nociceptor input have been suggested by studies in which dermatomal size and reactivity to stimulation has been shown to increase upon transection of nearby dorsal roots and/or Lessauer's tract. The observations, while not indicative of the locus of the modulatory effects, argue strongly for some form of regional interaction of nociceptive input, perhaps both tonic and evoked.

Data on electrical excitation of fibers in the ventrolateral tract provoking pain in man has been compared to similar data on fibers of antidromically excited cell bodies in monkey, as the basis of a contention that the "wide dynamic range" and multimodal cells of the deeper portion of the dorsal horn can provoke the experience of pain. This proposal assumes that the spinothalamic projections in man and monkey are quantitatively the same, as far as the size of the fibers and their respective characteristics, a point which is in doubt.

The trigeminal equivalent of the spinothalamic system is less well understood than is its spinal counterpart. The nucleus caudalis, particularly its more caudal spinal portion, is presumed to receive a major input from the nociceptive primary afferent fibers. The structure of the caudal part of the trigeminal nucleus is reminiscent of the more superficial portions of the dorsal horn; a marginal zone and substantia gelatinosa equivalent is underlaid by an apparent continuation of the nucleus proprius.

Nuclei of the reticular formation of the lower brainstem, such as the gigantocellularis and the ventralis reticularis, contain some neurons that exhibit nociceptive qualities and may be part of a nociceptive system, although at present evidence of their participation in mechanisms associated with sensory pain is lacking. A spinothalamic projection to the mesencephalic tegmentum has been demonstrated both morphologically and physiologically, and that part of this input reaching the periaqueductal gray matter surrounding the central canal has taken a special importance now that electrical stimulation in this region has been shown to exert potent effects upon various nociceptive reactions.

Three diencephalic regions receive significant projections from the spinothalamic pathways, and all three have been implicated in sensory pain. In primate, the principal somatosensory nucleus of the thalamus, the ventral posterior lateralis and ventral posterior medialis (ventrobasal complex), receive important input from the spinothalamic system that geographically overlaps the zones receiving a projection from the medial lemniscus. The spinothalamic distribution to the ventrobasal region differs morphologically from that of the medial lemniscus. Electrophysiological evidence of specific nociceptive neurons has been reported in ventrobasal complex. Recent morphological and electrophysiological studies have also emphasized another projection from the spinothalamic system to the medial thalamus. It reaches the vicinity of the centromedian and terminates in parts of the intralaminar group of nuclei (centralis lateralis and parafascicularis). Nociceptive responses by neurons in the intralaminar region and in what is called the centromedian (the exact limits given to this nucleus vary) have been reported in both animals and in man; they appear after a long latency, are related to activity in slowly-conducting myelinated and unmyelinated fibers, and fatigue readily.

It is believed that the cerebral cortex is not importantly involved in pain. Rarely, however, electrical stimulation of the cerebral cortex does apparently elicit reports of pain referred to the contralateral body. Several studies describe neurons in the primary somatosensory region. Particularly Brodmann's area 3 and in somatosensory area II that respond to noxious stimulation in a selective fashion. Such neurons comprise only a small fraction of the population recorded from anesthetized or unanesthetized animals with intact ascending sensory systems, but become more numerous when the dorsal columns and dorsolateral tracts are sectioned. Whether the emergence of this population following interruption of the input to the medial lemniscus represents a behavioral change in these neurons or rather the uncovering of a population masked by other projections is not known. The region of the cortex critical for nociception (area 3) is known to receive an input from the ventrobasal nucleus of the thalamus and it in turn projects back to the same thalamic region as well as to other parts of the cortex. The peculiarity of small lesions producing a deficit of pain perception while large lesions do not, has been argued to reflect the interaction in the

patterns of mutual excitation as well as inhibition of diencephalic structures and cortical areas.

Future trends: Knowledge of neural mechanisms of somatosensation is important not only because of its relevance to neural mechanisms of sensation in general but also because such knowledge will be important in the understanding of pain mechanisms. For example one of the thalamic nuclear group to be investigated is the intralaminar group. This nuclear group has long been implicated in sensation of pain because ablations in humans that include this region affect pain sensitivity and this region receives input not only from the classical pain pathways of the spinal cord but also from portions of the reticular formation and central gray that have also been shown to be involved in pain sensation. Any new information concerning the input to this region, therefore, will be relevant to the neural mechanisms of pain.

The theme of central modality segregation and electrophysiological characterization of quantitative properties in medullary and thalamic somatosensory neurons will be extended and amplified by anatomical studies of tracing projection neurons by using the method employing retrograde axonal transport of horseradish peroxidase. Electrophysiological mapping of specific mechanoreceptor representation in the thalamic ventrobasal complex will be performed in cats and monkeys using a chronic closed-skull preparation.
Examples of each receptor category will be subjected to extensive quantitive study of input-output functions.

The effects of electrical stimulus applied to the body surface, to peripheral nerves and to the spinal cord on the perception of experimentally induced noxious stimuli will be determined. The neurophysiological studies will be directed toward determining: (1) the action of various descending systems on the responses of spinothalamic neurons to naturally evoked peripheral stimuli, and (2) the segmental mechanisms by which these effects are mediated. Emphasis will be placed upon the action of the systems arising in the brainstem.

Physiological, anatomical and clinical studies suggest two major ascending pain systems originating from fibers in the mammalian ventrolateral spinal cord: (1) a direct spinothalamic system projecting to the posterior (PO) and intraliminar thalamus and (2) a spino-reticulo-thalamic system projecting via the medullary nucleus gigantocellularis (NGC) to the centre median parafascicular (CM-Pf) thalamic complex. If each pathway is necessary for normal pain sensation, lesions selectively interfering with transmission along either of these pathways should reduce behavioral responses indicative of pain. Accordingly, quantitatively controlled noxious and innocuous thermal stimuli will be used in an operant escape paradigm to test the long-term effect of lesions within the NGC, PO and CM-Pf of cats and squirrel monkeys. Threshold-independent increases in escape latency will be used to detect motor deficits precluding normal responses. The functional selectivity and long-term electrophysiological effects of such lesions will be examined by periodic evoked potential recordings from electrodes chronically implanted within PO and CM-Pf. Comparison of the behavioral and electrophysiological effects of the lesions should permit identification of the ascending system(s) necessary and/or sufficient for pain.

An experimental subhuman primate model of central pain has been discovered. Macaques have been observed to predictably multilate their hindlimp after undergoing a contralateral midthoracic anterolateral cordotomy of hemisection. Similar bizarre behavior has been observed in monkeys after total limb deafferentation. The same behavior occurred in one fortuitous case of a monkey with a pathological upper lumbar spinal syrinx. These phenomena suggest a remarkable parallel with the severe disturbing paresthesias in humans who had been subjected to the same neurological insult. The working hypothesis is that these phenomena result from interruption of transmission to and via the spinothalamic tract, which results in chronic abnormal discharge patterns at a diencephalic level. Various combinations of neurosurgery of spinal and peripheral levels have indicated that these paresthesias are largely independent of spinal mechanisms.

Brainstem mechanisms of trigeminal nociception are being investigated. The objective is to determine the relative involvement of each of four lower brainstem structures in the mediation of facial pain. These are: (1) the ventromedial border region of the trigeminal nucleus caudalis including the immediately subjacent lateral reticular formation, (2) the zona marginalis of the nucleus caudalis, (3) rostral medullary and pontine extensions of the lateral reticular formation and (4) the central core of the bulbar reticular formation. Two concurrent programs of research will be carried out. One will consist of acute electrophysiological experiments, principally with the cats, in which graded mechanical and electrical, noxious and innocuous stimuli will be applied to orofacial fields. Unit activity recorded extracellulary from responsive neurons in each of the four brainstem structures will be analyzed and quantified. Following histological verification to recording sites, data obtained from the four structures will be compared.

The other program will make use of two groups of waking unanesthetized monkeys with chronically implanted dental electrodes. Operant procedures will be used to obtain behavioral measures of pain induced by systematic, highly controlled stimulation of the tooth pulp through the electrodes. The measures will include escape thresholds and force of manual escape responses. Alterations in performance produced by discrete lesioning of the four brainstem structures will be studied in one of the groups of monkeys. Unit discharges evoked by pulp stimulation will be recorded from brainstem neurons of the other group of animals through indwelling, movable microelectrodes. Behavioral, anatomical and physiological data obtained from the two groups will be analyzed and compared. Ultimately the data will be used to provide a meaningful context for the interpretation of the results of acute electrophysiological experiments.

Endogenous Pharmacological Management of Pain

There are two main modes in pharmacological management of pain: exogenous and endogenous. The objective is to know what the endogenous substances are, how they are produced, where they are produced. What sensory system they affect and what their mechanisms of action are.

In the past decade, three major advances have been made in the area of pain research. First, neurons in the spinal cord dorsal horn involved in pain transmission have been identified. Second, brainstem sites have been discovered which produce profound analgesia when stimulated. Third, both opiate receptors and morphine-like peptides (endorphins) have been shown to be present in the vertebrate brain in areas that are important in analgesia production.

It has been shown that a neural substrate exists within the medial brainstem which serves normally to inhibit pain. This substrate may be activated by electrical stimulation or by morphine. Speculatively, it may be suggested that morphine acts directly at opiate receptor sites whereas electrical stimulation may, at least in part, act upon these sites indirectly via the release of the endogenous, morphine-like substance. The rationale for undertaking this kind of investigation is to develop modes of activation of this endogenous analgesic process without exogenously administering pharmacological agents. These developments evidently will lead to a better understanding of the nature of pain and may have a potential benefit in pain control.

There is now considerable evidence indicating that activity of neurons in discrete brainstem regions can strongly inhibit pain transmission. The first indication of this was the demonstration that electrical stimulation through electrodes implanted in the dorsal raphe nucleus and the mesencephalic periaqueductal gray in rats produces profound analgesia. Subsequent studies have demonstrated that analgesia can be produced in cats, subhuman primates, and man by stimulation of analogous brain sites.

Recent pharmacological studies are beginning to clarify the mechanism of opiate analgesia. Substances have been found in mammalian brains which bind morphine and other opiate drugs stereo-specifically and in rough proportion to their analgesic potency. In addition to this opiate receptor, compounds which show high and stereospecific binding to opiate receptor have been isolated from mammalian brain and subsequently identified and synthesized. These compounds, called enkephalins, are pentapeptides which have the pharmacological properties of opiate agonists. Enkephalins produce only brief analgesia unless structurally modified to prevent rapid degradation, or injected directly into the midbrain. Both enkephalin, and the opiate receptors are concentrated in discrete regions of the brain which overlap extensively. Moderately high concentrations of enkephalin and opiate receptors, are found in periventricular thalamus and mesencephalic periaqueductal grey, which are effective sites for electrical stimulus-produced analgesia (SPA). Also, when small amounts of opiates are injected into these regions, analgesia is produced. The overlap in mesencephalon and diencephalon of sites for SPA or opiate analgesia with regions of high concentraton of opiate receptors and enkephalin has raised the possibility that narcotics and electrical stimulation produce analgesia by a common mechanism, i. e., activation of an endogenous brainstem system. This system may operate under normal physiological conditions to suppress pain and is mediated by a descending control system arising in the brainstem which inhibits pain transmission neurons in spinal dorsal horn and trigeminal nucleus caudalis.

Opiate receptors: It has recently been established that there are opiate receptors in the vertebrate central nervous system. The presence of receptors has taken on even greater significance with the discovery of the endogenous brain ligands for it. Although the anatomical distribution of the opiate receptors varies in different species, there are many common elements. In most species the highest concentrations of opiate receptor are found in the striatum. In monkeys and humans, however, the limbic structures contain the highest levels with moderate levels in the striatum. All species studies have shown moderately high levels of receptors in the midbrain, especially the periaqueductal gray. Cortical levels are consistently low. Endorphins are found in multiple forms in the brain, e.g., leucine and methionine enkephalin and the pituitary hormone beta-endorphine, is a potent analgesic and strongly binds to the opiate receptors. In fact met-enkephalin is identical to part of the beta-endorphin molecule. Nevertheless, there is considerable overlap in the distribution of the enkephalin and opiate receptors. For example, in the rabbit, rat, and monkey, the highest levels of enkephalin are found in the striatum. Moderate levels are found in the midbrain and low levels in the cerebral cortex.

In summary, the areas of the brain where opiate peptides are produced or located and their anatomical distribution have been identified. Pain pathways specifically being affected have been worked out. Chemical characterization and their pharmacological implications seem to be underway, and opiate peptides-induced analgesia by electrical stimulation has shown analgesic action similar to that which is produced by morphine.

Future trends: During the past few years, several separate peptide substances have been structurally identified and shown to be present in significant quantities in the brain. Almost without exception, the highest concentrations of these peptides is in the hypothalamus, with particularly high concentrations in the neuro-vascular zone of the median eminence. Several of these peptides have clear functions in relation to anterior pituitary control; others, although shown in influence hormonal secretion, may function primarily in other regions of the brain related to sensory conduction, pain mechanisms, and behavioral responses. Receptors for many of these substances are now being searched for in brain tissues and pathways linking peptidergic systems are currently under investigation using neuroanatomical tracing techniques and immunocytochemistry. To achieve these objectives, research is being carried out with detailed analyses of: The neuroanatomy of peptidergic pathways, the neurophysiologic effects of peptides and a definition of their sities of action, neuropharacological studies to identify receptor sites on neural tissue and to identify agonists and antagonists that might have therapeutic implications, analysis of the hormonal and cerebrospinal fluid distribution and effects of peptides as well as the analysis of the behavioral effects produced by these substances.

Some of the aims directly or indirectly related to peptide analgesia with similar functional aspects will be emphasized; these include, the investigation of spinal cord mechanisms of stimulation-produced analgesia to learn more about the descending paths from analgesia-producing areas of the medial brainstem to the spinal cord sites of sensory inhibition. Also in this series of the experiments, the nature and locus of the inhibitory mechanism in the cord will be examined.

The interrelationship between normal biological states such as fear and the operation of the brainstem analgesia system will be investigated. There are two different major objectives to these studies: (1) To learn whether or not the analgesia system, in addition to blocking sensory transmission of nociceptive origin, also directly inhibits higher affective states such as fear which are associated with pain perception; and (2) that the pain inhibitory system lying within the medial brainstem is a normal, endogenous one, to ask the question of how biological states such as fear might affect the normal operation of this system. That is, if pain inhibition is the normal function of this system, what are the normal physiological accesses to this system which turn it on or off?

Further investigations are directed toward elucidating the role of the raphe nuclei in mechanisms of nociception and anti-nociception as well as the possible modulatory influence of other, monoamine-containing cell groups on the analgesia system.

Brain areas will be explored from which the analgesic effects of electrical stimulation are elicited and are not reversed by naloxone. It is likely that two different kinds of analgesic systems coexist in the medial brainstem, one which shares properties in common with morphine or an endogenous, morphine-like substance and hence is sensitive to naloxone and other which does not.

The phenomenon of morphine-mania will be invesigated with micro-injections of the drug into discrete brain regions, in the hope of learning something of general interest about morphine's mode of action by studying the peculiar response to this substance.

Recently, two morphinomimetic penta-peptides (methionine-enkephalin and leucine-enkephalin) have been synthesized. These will be tested in normal brain tissue by microinjecting these substances into discrete regions of the rat brain.

Experimental and Therapeutic Techniques for Control of Pain

Transcutaneous electrical stimulation: The importance of descending pathways in modifying the processing of sensory input is well known. Emphasis has been placed upon those interactions which occur at the spinal cord level. Interactions of this type have been specifically implicated in modifying the central action of noxious stimuli.

Since many of the descending pathways mediating these effects are also activated in the generation of motor behavior, it is likely that the resulting performances of motor tasks may affect the information processing of spinal inputs activated by both noxious and nonnoxious stimuli. These studies will provide insight into the degree to which motor behavior can modify the perception of noxious and nonnoxious stimuli which could be an index concerning the nature of perceptual changes induced in chronic pain patients. This procedure using externally applied stimuli could be employed in evaluation of therapeutic devices as well as for drug efficacy. For example, it will be worth examining the interaction of aspirin and transcutaneous electrical nerve stimulation with respect to their additive or supperadditive effects on the response of normal subjects to experimental noxious and nonnoxious thermal stimuli.

The evidence of interaction of salicylates (aspirin) and transcutaneus electrical nerve stimulation (TENS) is mediated by the endgenous opiate system, since it is reversed by narcotic antagonists such as naloxone. It is possible that TENS may produce analgesia indirectly by mobilizing the release of endorphins (precursors of endogenous opiates) in the spinal cord and that these in turn bind to opiate receptors. It has been found that, in patients with chronic pain, TENS elevated the level of endorphins in the cerebro-spinal fluid drawn from the part of the cord which received inputs from the region of the body to which the TENS was applied, whereas the level of endorphins in more distant parts of the cord remained unchanged. It has also been observed that a mixture of codeine and aspirin given orally produces a superadditive analgesic effect. These observations suggest that aspirin and TENS together might produce a higher level of analgesia than is possible with either alone. Therefore, a study is being conducted to determine if in fact the effects of aspirin and TENS are additive or superadditive and, if so, how this type of phenomenon is reflected in changes in variables assessed.

Use of Noxious and Nonnoxious Stimuli: The effects of the chronic pain state on the perception of thermal noxious and nonnoxious stimuli need to be determined to know whether a modification in the processing of sensory information has occured in individuals who have suffered from a chronic pain state. These patients are to be compared with the responses of patients with temperomandibular joint pain syndrome and tic douloureux in order to assess the extent to which chronic pain may modify both the discrimination of noxious and nonnoxious thermal stimuli. The rationale for this type of research would be to provide quantitative evidence that the clinical condition of chronic pain does in fact modify the CNS in such a way that the perception of acutely applied noxious and nonoxious stimuli is altered. This would further emphasize the importance of treatment programs designed not only to modify the behavior of chronic patients but also to treat the source of the chronic pain itself.

The experiments on the effects of chronic pain state on the perception of thermal nonnoxious and noxious stimuli are designed to examine long-term modifications of information processing in ascending sensory systems which may result from chronic pain. Given the potential of the central nervous system for localized trophic phenomena, it would not be surprising that a protracted chronic pain could be associated with long-term modifications in the activity of central pathways, which in turn might affect the perception of acute noxious and nonnoxious stimuli. Some evidence in the literature suggests that modifications of this type may in fact occur. Using a pressure algometer, it has been demonstrated that patients with substantiated organic basis for their pain had elevated thresholds to noxious stimuli applied with the algometer. Using a variety of noxious stimuli, including the pin prick, pressure algometry, and electric shock, it has been shown that hypochondiracs were extremely reactive to noxious stimuli, having a greater reactivity than normal subjects. However, the reactions of patients with organic pain varied depending upon their psychological state. For example, depressed patients with pain had elevated pain thresholds, while anxious patients with pain had decreased thresholds. Earlier work showed that the threshold for experimentally applied noxious stimuli decreased following relief of root pain in paraplegics, suggesting that modifications in perception can occur, not only when chronic pain is present, but also after it has been successfully treated.

Use of Implantable Stimulating Devices: It is also important to determine the effect of electrical stimuli applied with implantable stimulating devices to peripheral nerves and to the dorsal and ventral surfaces of the spinal cord on the perception of noxious and nonnoxious thermal stimuli. Because of the tremendous social and personal cost from causes of chronic pain, it is imperative that many possible therapeutic modes be assessed by which analgesia may be produced. Although there is currently a considerable lack of enthusiasm for the use of electrical stimulation techniques to modify pain perception, it is the consequence of inadequate evaluation of these devices using sound scientific methods. These psychopysical experiments can provide a strong data base for assessing precise features of pain perception. Because of the sensitivity of these measurements, their use could lead to employment in studies of appropriate stimulus parameters and stimulation sites to optimize the effectiveness of this technique in the management of clinical pain. They may even provide guidelines for the evaluation and subsequent utilization for producing analgesia in the CNS stimulation for producing analgesia

The use of implantable stimulating devices for producing localized analgesia has been attempted systematically since the gate theory was proposed. Despite the remarkable usefulness for this approach to treating chronic pain, very little has been done to quantitate the effects produced by these devices. Some of the preliminary data suggest that, under certain conditions and in certain patients, these implantable devices may produce marked therapeutic effects. However, further development of these devices requires more detailed information regarding the precise way in which they modify pain perception. In addition, factors pertaining to patient selection and the nature of pain problems treated by this technique may be much more objectively addressed if the relevant psychophysical data were available concerning the manner in which these devices actually affect the perception of noxious stimuli.

Current activities are directed toward determining if the perception of experimentally induced noxious and nonnoxious stimuli, as characterized by the measurement of discriminability using signal detection theory, can significantly alter pain perception. This approach discriminates psychological bases of pain from those of physiological origin. Using this technique, effects of electrical and thermal stimulation on chronic pain patients are being evaluated, such as effects of motor behavior on the perception of thermal noxious and nonnoxious stimuli, interaction of transcutaneous nerve stimulation and aspirin, effects of the chronic pain state on the perception of termal noxious and nonnoxious stimuli, and the effects of electrical stimulation applied with therapeutic devices on the perception of noxious and nonnoxious thermal stimuli.

Future directions involve investigation of safe and effective means of applying external stimuli and develop means of delivery of stimulus not only at the external surface of the body but in deeper specific regions of the CNS. Electric stimulation techniques seem to be superior to other procedures. They apparently are non-destructive of brain tissue and can be used repeatedly as the need arises. Other analgesic agents need to be developed to augment the therapeutic efficacy of the stimulation technique.

Surgical Control of Pain

Surgical procedures, especially on the CNS are considered a last resort when physical, pharmacological and even psychological procedures prove to be ineffective. Our current knowledge regarding regeneration and plasticity of nerve fibers is inadequate; once they are severed, they do not regenerate. For this reason,surgical procedures for relief of pain are performed only on terminal patients, such as those with cancer, or a situation where either sensory or motor function is not affected. In non-terminal patients, such surgical operations have also proved ineffective since pain sensation generally returns after six months to a year after such operations. The rationale for conducting these studies is to know why pain returns and what mechanisms are involved in these situations. Elucidation of these mechanisms would help a sizable proportion of the population including those who suffer from chronic pain, chronic low back pain, pain caused by a herniated disc, and pain caused by fibrous thickening, etc.

Recovery of pain reactivity following sequential lesions to the spinothalamic tract and other cord sectors of monkeys indicates that although the lateral spinothalamic tract of primates has been considered classically as the major pathway for ascending spinal conduction of pain, it has been known for some time that chronic pain sensation returns following chordotomy in humans. Recent physiological analyses of those spinal pathways receiving input from peripheral nociceptor elements has led to suggestions that each of the following pathways could participate critically in the recovery of pain sensitivity following chordotomy: the dorsal columns, Lissauer's tract, the spinocervicothalamic tract, the ventral spinothalamic tract, and the spinoreticular tract. To test these possibilities, unilateral chordotomies were performed on monkeys. Following recovery from contralateral analgesia, the other cord sectors were lesioned. The most pronounced deficits were observed when the chordotomy sectioned the entire ventral quadrant. The lesions that produced the most enduring secondary pain deficit was ventral hemisection. In contrast, a variety of dorsally placed lesions produced either no secondary dimunution of pain sensitivity or a transient effect. Clinically, surgical procedures have in some instances provided pain relief by spinothalamic cordotomy. A number of cancer patients have been helped by hypophysectomy by removal of the pituitary gland. Similarly, lesions placed in some areas of the upper brainstem have provided relief which in some instances lasts for several years.

Current activities include investigation of spinal somesthetic pathways of synaptic circuitry in the dorsal horn and other neurons, e.g., gelatinosa, nucleus magnocellularis; investigations of the source of those boutons which end on marginal neurons but do not degenerate following either multiple dorsal rhizotomies or Lissauer tractotomies; resolution of the issue of the level at which the spino-reticular relay takes place (medulla vs. mesencephalon) because this has major implications for the understanding of the nociceptive pathways both for the future experimentation and for the possible placement of chronic stimulating electrodes for control of pain in man.

Future emphasis is placed on investigation of pathways, neurotransmitters or other CNS mechanisms that can be surgically manipulated to control pain; search for clues to the involvement of hormones and hormonal glands, e.g., pituitary gland, in the control of pain; development of new microsurgical techniques and the improvement of the existing ones.

Pain Evaluation

There are at present several methods used in the evaluation of pain perception. Most of these techniques employ external stimuli such as heat, pressure or electrical impulses. These manipulations result in behavioral manifestations generally referred to as escape mechanisms of reflex actions. The degree of escape is then either measured by mechanical means or by physical displacement of limbs, such as tail-flicking, jaw-opening, reflex evoked by tooth pulp stimulation, avoidance behaviors in hot place test, paw-lick, flinch, jump, vocalizations, etc. In human studies there is an additional advantage or disadvantage in that the pain experiences elicited by physical means cannot be objectively evaluated. These experiences are invariably influenced by the psychological state of the person involved. On the other hand, the advantage is that the responses to the experience can be communicated verbally. The rationale for pursuing these studies is to devise sound and reliable methods by which response to any stimulus or analgesic agents can be evaluated objectively without being influenced by human emotions.

Current State of Knowledge: One of the most difficult problems facing the experimenter who wishes to study the psychophysics of pain perception is determining the method by which the stimulus is to be reported by the subject. In order to objectify the responses to noxious stimuli, some investigators have assessed the autonomic responses which are evoked. However, changes in physiological parameters may be uncorrelated with the subject's verbal assessment of the noxious stimulus. Moreover, certain physiological indicators which have been employed, such as grimacing, are likely to be at least as variable as verbal reports by the subject. The use of autonomic changes has the additional drawback of reflecting activity in specific reflex pathways which may not be related to alterations in supratentorial interactions which are felt to play a role in nociception. Therefore, if only these responses are measured, some important differences between the moderate stoic and the moderate hysteric might not be discernable.

Although it has been argued that the use of verbal reports may be extremely unreliable, these reports may provide the most important and hence most valuable source of information about the pain experience. The use of a dolorimeter suitable for applying quantitative thermal stimuli made it possible to use the verbal report of a subject in response to measurable amounts of thermal energy applied to the skin surface as the basis for developing a quantitative psychophysical assessment of pain perception. Although it was possible to demonstrate that the dol scale had a firm psychophysical basis and correlated with other measurement of pain perception, the use of this method for quantifying the verbal response of the subject has not been widely used. In addition to the experiments examing responses over an entire intensity continuum, attempts were made to evaluate Pain thresholds using a method of limits or a constantly increasing or decreasing stimulus. To reduce the variability that commonly occurs when using these techniques for evaluating pain perceptions and its alteration due to the action of analgesic agents, pain tolerance tests were developed. Studies assessing the analgesic action of morphine and morphine derivates emphasized the value of using pain tolerance under some conditions, in addition to the traditional pain threshold measurements. Variations of these techniques such as the use of the cold pressor pain have also been employed.

Although the use of these methods has yielded very valuable information, certain inadequacies became apparent. These inadequacies related principally to the difficulty in utilizing these measurements to gain an understanding of the psychophysical processes involved in nociception rather than an inadequacy in demonstrating changes *per se* in the response to pain by various therapeutic and experimental procedures. First the variability in the absolute measurement of pain thresholds among subjects was considerable. The second and perhaps major limitation of the methods employing the assessment of pain tolerance and pain threshold is that the complex psychophysical process underlying nociception is represented by only one measurement. It is generally agreed that the report of pain is a function not only of the actual sensory experience, but also of the subject's tendency to bias his description of what he perceives. In a study of nociception, it would therefore be desirable to have means of assessing both of these factors. One attempt to assess the sensory component of the pain experience, independent of response bias, has involved the use of signal detection theory. As it is applied to psychophysical studied, two independent variables can be calculated from the data base. The first, usually referred to as discriminability which is a measure of the subject's tendency to distinguish between two different stimuli. The second variable is the likelihood ratio or criterion, which reflects the "rules" by which the subject assigns a certain description to a given sensation. Because signal detection theory has proven to be useful in other psychophysical paradigms as a means of dissociating changes in the cognitive and sensory components of a response into change in criterion and discriminability respectively, several investigators have attempted to adapt this method to the study of nociception and analgesia.

Other compounding factors: Application of signal detection theory to the assessment of pain and evaluation of analgesic drugs has been criticized from several points of view. However, in the absence of any available method by which one can realistically evaluate magnitudes of pain unrelated to psychological influence, this theory comes closest where apparent bias may be ruled out. Several studies have been conducted which show that the difficulty lies not only in the assessment of true pain experience alone, but pain experience can also be altered by environmental factors such as physical distraction, sound, etc. This further compounds the problem of pain assessment. Some of the compounding factors are given below. The importance of suggestion has been emphasized in modifying certain aspects of sensory perception. In studies of nociception, the effects of suggestion, particularly placebo effects have been considered. Most of these studies are directed toward determining the analgesic effect of suggesting to the subject that a device, drug or type of manipulation may actually produce a modification in pain perception. Many studies have shown that, if the patient believes that a certain procedure or compound will modify his sensory experience, a modification will indeed occur. However, the data also suggest that the specific perceptual changes induced by the placebo may be different from those produced by the actual substance or procedure. Moreover, the effects of suggestion on the specific quantitative changes in the variables assessed using a signal detection theory analysis can be different, depending on the type of suggestion and the paradigm in which it is employed.

The problem of suggestion was examined from a different perspective. Rather than suggesting verbally to the subject the direction of a probable analgesic effect, sham electrical stimulation was applied using neutral instructions. Under these conditions, the "suggestion" that electrical stimulation was actually being applied resulted in a change in discriminability rather than in criterion. Together, the results from all of these studies imply that the effect of suggestion is dependent upon the nature of the suggestion *Per se* as well as the paradigm in which it is employed.

Studies have demonstrated that hypnosis also affects pain perception. Several speculations have been made concerning the mechanism by which this effect is mediated. The studies demonstrated that the analgesia produced by hypnosis is very likely unrelated to the mechanism by which a placebo produces analgesia. In fact, it was demonstrated that subjects who were easily hypnotized had a much more marked analgesia and smaller placebo effect than those who were more difficult to hypnotize. The "analgesia" produced by the placebo, however, was comparable to that occurring mechanism of hypnosis but is not related to either a placebo effect or to the fact that there may be a reduction in anxiety associated with hypnosis. Rather it is attributed to the analgesic effect to a transient amnesia or disorientation phenomenon produced by this procedure. It is shown that a marked analgesia to cold pressor pain could be produced by hypnosis under conditions in which the subject was capable of objectively reporting the intensity of this stimulus. The fact that mechanisms underlying the analgesia produced by hypnosis are, in fact, due to mechanisms other than those related to the action of morphine is supported by the finding that hypnotic analgesia effects were not reversed by naloxone.

Anxiety has also been shown to produce an alteration in nociception. In the very early studies the presence of anxiety induced by the stimulus paradigm was found to be associated with an increase in the reaction to noxious stimuli. The effect of anxiety may in part be due to the resulting distraction. The effect of distraction produced by three techniques was examined: a story, an additional task, and a counting task. It was found that if the story or the additional task were presented throughout a two minute period of painful stimulation, a reduction in the report of pain and a reduction in the percent time that the subjects reported attending to the pain was observed. The fact that distraction may also decrease at least the awareness of clinical pain has also been emphasized. It has been shown that auditory stimulation, particularly when accompanied by suggestion, produced alterations in pain perception. For example, the application of auditory stimuli produced an elevation in the amount of electrical stimulation that had to be applied on the dorsal surface of the forearm in order to evoke a report of pain. The effect of distraction was produced not only by sensory stimuli, but sensorimotor tasks as well. It was found that the phantom limb pain was reduced by the use of sensorimotor tasks as well as by nonnoxious sensory stimuli when applied repeatedly throughout the rehabilitation of the patient.

NEUROENDOCRINE STUDIES

Currently this program supports 58 projects related to steroid hormones, neuropeptides and interaction of these endocrine systems with monoamine neurotransmitters. Most of these projects deal with the identification of hormone receptors and neurosecretion. Also included are related phenomena such as synthesis, storage, release, transport, conversion, inactivation, regulation, and characterization of the neuroendorine peptides in the brain, hypothalamus and pituitary. Some projects study neuroendocrine functions as related to behavior, thirst, hunger, body weight regulation, circadian rhythms, stress, temperature regulation, etc. The total expenditure in this subprogram is $4,131,926.

During the past few years many separate peptide substances have been structurally identified and shown to be present in significant quantities in the brain. Almost without exception, the highest concentration of these substances is in the hypothalamus, with particularly high concentrations in the neurovascular zone of the median eminence. Several of these peptides have clear functions in relation to anterior pituitary control; others, although shown to influence hormone secretion, may function primarily in other regions of the brain related to sensory conduction, pain mechanisms, and behavioral responses. Receptors for many of these substances are now being searched for in the brain. Pathways linking peptidergic systems are currently under investigation using neuro-anatomical tracing techniques and immunocytochemistry.

Occurrence of Neuropeptides

The hypothalamic releasing and release-inhibitoy hormones, which serve a neuroendocrine function to regulate anterior pituitary-hormone secretion, have a wide distribution throughout the CNS that is compatible with their additional postulated behavioral roles. The same is true for the posterior pituitary peptides, vasopressin and oxytocin, which are found in extrahypothalamic fiber projections in addition to the hypothalamic-neurohypophyseal system, where they were originally localized. A number of peptides originally found in secretory elements of the gastrointestinal tract, including substance P, cholecystokinin (CCK), and vasoactive intestinal polypeptide (VIP), are now described as occurring in both endocrine and nerve cells in the gut and in the brain.

As additional peptides are described in the brain because of advances in modern procedures for their purification, sequencing, and synthesis and because of the development of antibodies for radioimmunoassays and immunocytochemical studies, it is essential to validate the methods used to detect them and to ascertain whether the form or forms identified in the CNS are identical to those present in the initially described site of origin. In attempting to assign a functional role for each peptide, it is also necessary to determine whether they are synthesized in the brain or occur there as a result of vascular transport - either from the general circulation or, in the case of the pituitary hormones, through retrograde circulation in the pituitary portal venous system.

Several projects are investigating the distribution of several biologically active peptides in the brain, spinal cord, and pituitary gland. The following peptides are being be studied: Substance P, neurotensin, thyrotropin releasing factor, gonadotropin releasing factor, somatotropin releasing factor or somatostatin, melanotropin release inhibiting factor, alpha-melanocyte stimulating hormone, the opioid peptides: enkephalins and endorphins, etc. The peptides are being localized with the help of specific antibodies. Thus the sensitivity and specificity of the immunochemical binding is combined with the structural resolution of light and electron microscopy. This permits precise topographical localization and mapping of the peptide-containing cells, pathways and synaptic contacts in the brain. Most of the peptides to be studied have been discovered only recently. Initial work indicates their widespread distribution throughout the body, but especially in the nervous and endocrine systems. They may function as neurotransmitters, modulators of neurotransmission, regulators of hormone release from the pituitary gland, or as neurohormones released directly into the blood stream. In order to conduct meaningful physiological studies with these peptides, knowledge on their precise cellular and subcellular localization as well as topographical distribution in the central nervous system will be essential.

Peptide Receptors

The role of peptides in neurobiological function has received increasing attention in recent years. It appears that most peptides are distributed widely throughout the brain and act by attachment to peptide receptors to initiate neurobiological events; these effects result in neurophysiological, biochemical, and behavioral manifestations. The presence of peptides in the CNS has stimulated intense interest in uncovering cellular receptors for them. Current studies are directed at determining whether such receptors exist, the nature of their localization (i.e., presynaptic, postsynaptic, or in blood vessels), whether their distribution coincides with that described for the peptide, and whether more than one type of receptor is present for a given peptide form or forms. At present, save for the opioid receptors, this field remains in its infancy. Identification of two types of opiate receptors according to binding characteristics and by bioassay has occurred in parallel with the demonstration of multiple types of opiate substances present within the nervous system. These observations have served to illuminate the diverse physiologic functions of the endogenous opioids. It appears that there are at least two types of opiate receptors, called mu and delta. It is likely that mu receptors are involved in mediating analgesic responses, whereas delta receptors are involved in eliciting seizure activity and in certain behavioral responses. Endorphin appears to bind to both types of receptors; the enkephalins bind only to mu receptors. Morphine binds predominantly to mu receptors, and it has been suggested that dynorphin, which is vastly more potent may be the endogenous ligand for the mu receptors. It has been possible to characterize the differential distribution of delta and mu opiate-receptor localization within the CNS by autoradiography and with the light microscopy.

It was recognized over two decades ago that mammalian neurons synthesize and release peptides in addition to the putative neurotransmitters. Since then, at least 10 classes of peptides active in the CNS and periphery have been identified. Bombesin (BN) represents one such class of peptides active in the central nervous system (CNS) and gastrointestinal (GI) tract. While the physiological importance of BN-like peptides is not known, endogenous BN-like peptides may interact with receptors which are present in the CNS and GI tract. Further, both the endogenous BN-like peptides and receptors in the CNS are localized to synaptosomes. In this regard, upon receipt of appropriate depolarizing stimuli, BN-like peptides are released from rat brain slices in a Ca-dependent manner. While the relationship of BN-like peptides and receptors to a particular neurological disorder is premature at this time, these peptides may function as important neurotransmitters.

The functional significance of specific prolactin binding sites on ependyma of the rat choroid plexus is being investigated with emphasis towards a possible role for prolactin in the regulation of electrolyte balance between blood and cerebrospinal fluid (CSF). A preliminary electron microscopic autoradiographic analysis of prolactin movement relative to ependyma cytology indicates initial binding of prolactin to ependyma plasmalemma within a very short time. These results suggest that ependyma may be the final target cells rather that a component of a blood to CSF transport system for prolactin.

Brain cells are protected from the effects of circulating peptides by the brain endothelial wall, i.e., the blood-brain barrier (BBB). The available evidence indicates specific transport systems in the BBB, similar in nature to carrier systems known to transport nutrients and thyroid hormones, do not exist for peptides. There is evidence, however, that specific receptors for circulating peptides such as insulin do exist on the luminal side of brain endothelia. Peptide binding to the BBB may generate the production within endothelia of second messenger compounds that are released to brain extracellular space; in this way mechanisms would exist for the rapid modulation of brain cell function by circulating peptides, without the peptide actually crossing the BBB. Studies are examining peptide binding and action at the BBB using the isolated cerebral capillary as the primary model system. Three major areas will be investigated. The specific binding to isolated capillaries of such peptides as insulin, enkephalins, vasopressin, somatostatin, angiotensen II, and prolactin, are being studied and second messengers as cyclic AMP, cyclic GMP, glycine, glutamate, aspartate, or GABA, will be investigated which affect the peptide-mediated release of these substances into the brain.

Neurosecretion and Biosynthesis of Peptides

The most detailed studies of biosynthesis and neurosecretion of CNS peptides have been performed with vasopressin and with the pro-opiocortin-ACTH and B-lipotropin (B-LPH) peptides. In the case of vasopressin, these studies have provided the basis for the concept of neurosecretion as originally described. In the case of ACTH, such studies provide evidence for similar synthetic mechanisms for peptides in two different areas (CNS and pituitary). In both instances, it is apparent that peptides are synthesized as larger precursor molecules that undergo further processing before secretion, providing evidence for a common mode of biosynthesis for secretory proteins and peptides in both endocrine and neural tissues.

Neurosecretion

The process of neurosecretion has been of considerable interest since E. Scharrer pointed out the existence of "glandular neurones" in the hypothalamus of mammals and suggested that the hormones of the posterior pituitary might be synthesized by these neurons in the hypothalamus. Since these pioneering observations, active studies in many laboratories have produced a voluminous literature on the structure and function of neurosecretory systems. In recent years interest in the neurosecretory process has taken on new momentum and dimensions. The classical concept of neurosecretion has been expanded as a result of new findings. With the discovery that neuronal tracts containing peptide hormones are found widely spread through the central nervous system, that many peptide-producing neurons do not have their axonal projections directed to organized neurohemal organs, and that many peptides have direct electrophysiological effects on neurons, the importance of peptide hormones as neruotransmitters or neuromodulators is being actively explored. In addition to humoral pathways and direct innervation of target neurons, a third avenue of peptide hormone action has received considerable attention: the prevalence of neuroactive peptides in the various circumventricular organs has implicated the cerebrospinal fluid as a pathway for peptide action in the central nervous system. Thus, with the realization that neurosecretion is a much more widespread phenomenon than previously realized, the discovery of new neurosecretory compounds (e.g. endorphins), and the discovery of many new roles for previously defined hormones, neurosecretion has become an important focus in the neurosciences and in the study of human physiology in general.

Studies on the Synthesis of Neurosecretory Hormones

Although the focus of research on neurosecretion has been on morphological and physiological studies, the biochemistry of the neurosecretory process has not been studied so extensively in the vertebrate systems. Most of the studies on the discrete biochemical stages of the process have been performed on the hypothalamo-neurohypophysial complex. The first direct chemical demonstration of the biosynthesis of a neurosecretory hormone was performed by Sach in 1963 who demonstrated that after infusion of ^{35}S-cysteine into the third ventricle of the dog, labeled vasopressin could be isolated from the hypothalamus, and that although some labeled hormone could be found in the neural lobe, the specific radioactivity of the hormone there was much lower than that in the hypothalamus. This subsequently provided indirect evidence for the involvement of a prohormone in vasopressin synthesis. Since then information derived from work with other peptide producing tissues has suggested that a high molecular weight precursor to active peptide processing is a common, if not universal, feature of biosynthesis of neurosecretory material.

Neurotransmitters and Neuropeptide Secretion

Although it is well known that neurotransmitters play a prominent role in the regulation of hypophyseal hormone secretion, their site of action is unclear. The neurotransmitter effect may be a direct one with the neurotransmitter itself stimulating or inhibiting hormonal release from the pituitary gland. Alternately, its effect may be an indirect one by modulating the release of specific hypothalamic releasing or inhibiting hormones. Studies are being conducted to determine the actions of the neurotransmitter dopamine on pituitary hormone secretion with emphasis on prolactin (PRL) and growth hormone (GH) release and to ascertain whether hormonal secretion is affected by direct (peripheral) action on the petuitary gland, by hypothalamic or higher center actions (central) or by actions at both levels.

It is well accepted that the hypothalamic regulation of anterior pituitary hormone secretion is mediated by vascular and not neural connections and that neurotransmitters play an important role in modulating this secretion. Furthermore, because of the anatomic arrangement of the blood supply of the median eminence and pituitary, these structures can be affected by peripherally administered or secreted test substances and hormones, as well as through central nervous system actions.

There is a great deal of evidence that the biogenic amine, dopamine (DA), affects pituitary function in the human. This effect is more pronounced on PRL and GH secretion. DA has recently been shown to also blunt LH secretion in healthy women and men. An effect on corticotropin (ACTH) and thyrotropin (TSH) in normal subjects is more subtle, but under extreme endocrinologic perturbations it is readily apparent.

Although there is considerable in vitro and animal data to demonstrate an inhibitory effect of DA on prolactin release, the data on whether this is a direct pituitary effect or mediated via hypothalamic prolactin inhibiting factor (PIF) release are conflicting. Prolactin secretion by the anterior pituitary gland is largely controlled by a hypothalamic prolactin inhibiting factor (PIF), whose chemical identity has been debated until recently. Evidence based on the following findings suggest that dopamine of hypothalamic origin serves as a physiological PIF: a. The demonstration of dopaminergic pathways in the median eminence and the neurohypophysis. b. The presence of dopamine in hypophysial portal blood at higher concentrations than in the systemic blood. c. The demonstration of reciprocal relationship between hypothalamic dopamine secretion and anterior pituitary prolactin release under a variety of endocrine states. d. The ability of dopamine and its precursors and agonists, to inhibit prolactin secretion both in vivo and in vitro. e. The identification of specific dopaminergic receptors in the anterior pituitary gland.

Most researchers today agree that a substance shown to fulfill all of these criteria can be considered as a true hormone. However, in view of the multiplicity of factors associated with prolactin release, the reassessment of the anatomical-functional importance of the hypophysial portal vasculature, and the many unanswered questions regarding the characteristics of anterior pituitary dopaminergic receptors and the mechanism of inhibition of prolactin secretion, the following question are being investigated: Is dopamine a dynamic regulator of prolactin secretion and is PIF activity in tissue extracts and portal blood attributable to dopamine? How does the posterior pituitary participate in the regulation of the secretion of prolactin and other pituitary hormones? What are the characteristics of dopaminergic receptors on pituitary lactotrophs in terms of localization, metabolic and ionic requirements for binding and possible changes in their affinity and/or density which might reflect different physiological states? By what mechanism does dopamine inhibit the secretion of prolactin and what are the possible roles of changes in the electrical activity of cell membrane and the availability of calcium ions?

Growth Hormone

In the human, the effects of L-dopa on GH secretion are equally marked, although in the opposite direction. The original observation that GH increased in patients with Parkinson's disease following administration of L-dopa has been extended to normal subjects, and L-dopa has become a standard provocative test for the evaluation of pituitary function. The administration of the dopamine agonist, apomorphine, has also been shown to cause GH release. Interestingly, in patients with exceesive GH secretion due to pituitary tumors, i.e., acromegaly, L-dopa has a paradoxical effect and causes a marked decrease in GH concentration. Indeed, it is this property that has led to the successful use of the dopamine agonist, bromoergocryptine (CB154) for treatment of this condition. Nevertheless, while the responsiveness of GH secretion to changes in DA concentration is apparent in both normal subjects and in acromegalies, albeit in opposite directions, the mechanism and site of this action are not clear.

Experimentally, the dopaminergic tuberoinfundibular neurons (TIDA) are generally believed to have an important role in the regulation of the secretion of the anterior pituitary, particularly in relation to prolactin release. On the other hand, the hormonal and the hypothalamic neurotransmitter inputs to the TIDA neurons and the influence that these inputs have on the activity of the TIDA neurons have not been extensively investigated. Identification of some of the hormonal and neurotransmitter input to TIDA neurons will provide significant insight into the next higher level of the hypothalamic control of anterior pituitary function. The objectives of these studies are to investigate possible noradrenaline (NA), serotonin (5-HT), leuteinizing hormone releasing hormone (LHRH) or luteinizing hormone (LH) input onto TIDA neurons. In separate studies each of the above agents will be infused into the 3rd ventricles of female rats via a permanently implanted guide tube. The effects of this treatment on the content and turnover of DA in the arcuate nuclei, median eminence and intermediate lobe-neurohypophysis complex will be determined with the use of extremely sensitive analytical methods for DA quantitation. These specific hypothalamic and pituitary regions represent the sites of origin and termination, respectively, of TIDA neurons. Subsequent experiments will determine if effects of these agents are directly on TIDA neurons, whether these effects are mediated within the medial basal hypothalamus and whether the effects are influenced by gonadal steroids.

Clinical Implications of Prolactin Secretion

As alluded to earlier, DA (or PIF) inhibits the release of prolactin, the release of leutinizing hormone (LH), on the other hand, is inhibited by prolactin. This evidence comes from several physiological states in which an inverse relationship has been observed between these two pituitary hormones. The clinical implications, based upon these inter-relationships are obvious. It points to the fact that prolactin may suppress the neuroendocrine mechanism for cyclic LH/FSH secretion and may thus be responsible for the inhibition of ovulation prior to or during lactation. This anatogonism has profound contraceptive significance. Roger Shoot, in his book, proclaimed these prophatic exclamations:

> "There can be no doubt that hitherto breast-feeding has been the major factor holding human population growth in check; even today, it probably prevents more pregnancies the world over than all artificial forms of contraception put together — we need to provide (the mother) with some form of contraception that will mimic the natural inhibitory effects of lactation on reproduction, and allow her a respite of several years of amenorrhea between successive pregnancies. Lactation has always been the central controlling mechanism for the regulation of reproduction in mammals. In our species, we could now assist nature by developing contraceptives specifically to stimulate lactation."

Based upon this information contraceptive strategies could be evolved which involve the suppression of the midcycle LH/FSH surges with prolactin or its analogues which are potent, specific and short-lasting dopamine antagonists. Not only are the great potential to benefit of this system in the reproductive biology, there are far reaching implications in treating other neurological disorders. For example, drugs that lower prolactin such as L-DOPA and bromergocryptine have recently been used in the management and treatment of the galactorrhea-amenorrhea syndrome. This bears directly on the physiological basis of its therapeutic actions in the treatment of the amenorrhea-galactorrhea syndrome, regression of PRL-secreting tumors, Huntington's disease, dyskinesias, geriatric disorders and parkinsonism. The action of such drugs may well rely upon the neuroendocrine mechansim regulating PRL secretion which is known to involve dopaminergic neurons. Basic knowledge about this mechanism, particularly its physiological regulation, would be invaluable in the interpretation of clinical results and in the development of more specific pharmacological agents with unique actions on dopamine metabolism.

Vasopressin and Oxytocin

The large (magnocellular) neurons of the hypothalamic supraoptic nuclei and paraventricular nuclei (PVN) have provided a unique model for the study of peptide neurosecretion in the brain. Unmyelinated axons derived from these cells traverse the basal hypothalamus to terminate in the median eminence and neural lobe. It was from extracts of the posterior lobe of the pituitary that the nonapeptides vasopressin and oxytocin were isolated.

The two peptides are produced in separate cells; both types of cells are distributed within the supraoptic and PVN nuclear groups. The morphologic counterpart of the secretory product of the magnocellular neuron is a dense-core granule measuring 150 to 300 nm in diameter. The granules, which can be identified in the cell body, axon, and terminal, contain either vasopressin or oxytocin and the corresponding neurophysin, and probably a larger precursor molecule or molecules as well. By definition, neurosecretory cells like other neurons, generate depolarization potentials that regulate release of the hormonal products from nerve terminals. Converging inhibitory or excitatory afferents from other brain regions regulate neurosecretion to achieve neuroendocrine control. Neuronal depolarization results in release of the entire granular contents into the perivascular spaces, where diffusion into the blood rapidly occurs. In the case of vasopressin, current evidence indicates that the hormone is released from the neural lobe into the systemic circulation and also into the median-eminence portal capillaries to reach the anterior lobe.

Recent anatomic observations indicate that the hypothalamic magnocellular neurons are capable of two additional forms of secretion. Axon terminals with identified secretory granules can be traced between ependymal cells lining the third ventricle to end blindly in the cerebrospinal fluid (CSF). Arginine vasopressin can be detected in the CSF by radioimmunoassay, and it has been speculated that CSF distribution may have functional importance. Another anatomic pattern of distribution of the hypothalamic neurosecretory system, which arises primarily from the PVN neurons, is extrhypothalamic, with termination in the septum and thalamus, the locus ceruleus and nucleus tractus solitarius of the brain stem, and the dorsal and intermediate gray matter of the spinal cord.

Earlier it was proposed that vasopressin and its associated neurophysin were synthesized together as a common precursor by neurons of the supraoptic nucleus. Subsequent studies confirmed that vasopressin and oxytocin were derived from separate precursor forms that also gave rise to two neurophysins. This precursor is modified during transport down the axon into molecular fragments that included the neurophysins (molecular weight, about 10,000 daltons) and smaller substances corresponding in size to oxytocin and vasopressin. Limited proteolysis of the labeled precursors with trypsin and characterization of the fragments gave components that were identified as the neurophysins, vasopressin, and oxytocin.

Somatostatin

Somatostatin, a tetradecapeptide (14 amino acids) that was first isolated from sheep hypothalamus, exists in a larger precursor form in the brain and gut. The same larger molecule has been isolated from ovine hypothalamus. Current evidence suggests that somatostatin biosynthesis in the brain, pancreas, and gut occurs by formation of a precursor with a larger molecular weight. Separation of immunoreactive somatostatin from brain extracts indicates that two precursor forms exist. Similar heterogeneity is found in the median eminence of the hypothalamus, in the preoptic area, and in the amygdala and cerebral cortex in the rat. Purification of hypothalamic messenger RNA coding for somatostatin yielded evidence that the primary translation product is a 15,000-dalton species. Taken as a whole, these observations support the idea that somatostatin, the prototypic brain-gut hormone, is synthesized by comparable mechanisms in the two tissues. It will be of great interest to determine whether the genetic regulation of somatostatin biosynthesis is identical or dissimilar in tissues that are derived separately embryologically.

ACTH and Related Peptides

It is now recognized that ACTH and beta-LPH, which were intially isolated separately from anterior pituitary extracts, are derived from a common precursor molecule. This precursor also contains several recurrent sequences identified as alpha, beta and gamma -melanocyte-stimulating hormone (alpha, beta and, gamma -MSH). The peptide beta -endorphin corresponds to residues 61-91 of beta -LPH.

Activities like those of ACTH, alpha -MSH, and beta -MSH in neural tissue were first shown in extracts of hog and dog hypothalamus. Later ACTH was found both in the hypothalamus and in other areas of rat and bovine brain and showed its persistence in the CNS after hypophysectomy. After demonstration of the precursor molecule for ACTH and related peptides in pituitary tissue, it was shown that a similar precursor exists in the brain and that other peptides derived from it (alpha -MSH, beta -LPH, and beta-endorphin) are also present.

The demonstration of a peptide in a tissue other than its previously described primary site of origin requires proof that synthesis occurs in the new site and documentation that synthesis and processing are similar or dissimilar in the two tissues. Studies were initiated with dispersed hypothalamic-cell preparations of arcuate neurons that had been shown to contain ACTH, beta -LPH, and alpha -MSH. Such preparations, maintained in culture, secrete immunoreactive ACTH and beta -endorphin-like material into the medium in a nearly linear fashion without any notable change in cellular peptide content. In subsequent studies, hypothalamic cells in vitro synthesized high molecular weight tritium-labeled material containing both ACTH and beta -endorphin. Such material was similar to precursor material synthesized in the pituitary in size and heterogeneity. Tryptic digests of the high-molecular-weight material from the brain yielded peptides containing the ACTH and beta -LPH regions of the molecule; these peptides were similar to those derived from tryptic digests of the anterior-pituitary precursor molecule. These studies indicate that synthesis of the precursor material is similar in the hypothalamus and pituitary.

In addition to synthesis of material of high molecular weight, incubated rat hypothalamic tissue also yields products similar to those of beta-endorphin and alpha-MSH, as well as lesser amount of beta-LPH and ACTH 1-39. In the anterior pituitary the precursor molecule is processed predominantly to ACTH and beta-LPH, whereas in the intermediate lobe ACTH and beta-LPH are further processed to alpha-MSH and beta-endorphin-like material, respectively. It therefore appears that in the hypothalamus, the processing of the precursor molecule more closely resembles that in the intermediate lobe but is not identical to it.

Other neuropeptides: The various categories of peptides found in the CNS are indicated in the following table:

Hypothalamic releasing hormones
Thyrotropin-releasing hormone (TRH)*
Gonadotropin-releasing hormone*
Somatostatin*
Neurohypophyseal hormones
Vasopressin*
Oxytocin*
Neurophysin(s)*
Pituitary peptides
Adrenocorticotropic hormone (ACTH)
  Endorphin*
  Melanocyte-stimulating hormone
    (MSH)
Other pituitary peptides**
Prolactin
Growth hormone
Luteinizing hormone
Thyrotropin

Gastrointestinal peptides
Vasoactive intestinal polypeptide (VIP)*
Cholecystokinin (CCK-8)
Gastrin
Substance P*
Neurotensin*
Methionine enkephalin*
Leucine enkephalin*
Insulin
Glucagon
Bombesin
Secretin
Somatostatin*
TRH*
Others
Angiotensin II
Bradykinin
Carnosine
Sleep peptides(s)
Urotensin I & II

*Peptides first isolated and characterized in the central nervous system.
**Not yet conclusively demonstrated in brain.

As described earlier some of them are being investigated intensively while others are at various stages of investigation. Application of organ tissue culture techniques has demonstrated great potential in elucidating the mechanisms involved in many of the stages of neurosecretion, biosynthesis, degradation and release processes. In general, studies both *in vitro* and *in vivo*, are designed to answer the fundamental question, such as: What controls the synthesis of hormones in neurosecretory cells? What is the relationship between synthesis and neuronal stimulation or inhibition? Does released hormone feedback directly to afftect synthesis? Does pro-hormone processing have a regulatory role in active peptide production? What is the relationship between peptide hormones and proteins which are generally considered to be their carrier proteins? Is synthesis carried out entirely in the neuronal perikaryon before packaging into vesicles in the golgi apparatus, or does the hormone "mature" in the neurosecretory granule? What is the nature of the process by which neurosecretory granules are transported to storage and release sites? How are hormones stored? Does more than a single storage pool exist? What controls release of the hormones? Are synthesis, stimulatin, transport and release all closely coupled, or are they under independent control?

Peptide Processing and Degradation

With the demonstration of prohormones for many of the peptides present in the brain (i.e., "pro-opiocortin," neurophysin-vasopressin, enkephalin, somatostatin, and TRH), the importance of the role of proteolytic enzymes in the processing of the prohormones to active component forms is becoming increasingly evident. There are two general categories of proteolytic enzymes; exopeptidases and endopeptidases. Exopeptidases that act on the substrate peptide at the N-terminus are called aminopeptidases if free amino acids are released (such release requires a free-NH_2 terminus) and are called dipeptidyl aminopeptidases if intact peptides are released. Exopeptidases that act on the free, unsubstituted C-terminus are called carboxypeptidases if free amino acids are released and peptidyl dipeptidases if intact dipeptides are released. Endopeptidases cleave specific internal bonds; this type of bond may also be cleaved when the specific bond is formed with a free amino acid. The endopeptidases are involved in activation of precursor hormones with formation of active products, whereas both exopeptidases and endopeptidases may be involved in peptide degradation and termination of hormone action. From existing studies, it appears that unlike the uptake mechanisms that are available for terminating the actions of the classical neurotransmitters, termination of action of released peptides is effected by peptidase action. Endogenous protease inhibitors are also present in tissues, and it is possible that factors regulating their activity may have important roles in the regulation of the peptides on which they act in normal and abnormal physiological conditions.

Of the known exopeptidases and endopeptidases, only a small number have been characterized in the CNS, and few of them have been prepared in purified form. The specificity of many of these enzymes for particular brain peptides has not been established.

Regulation of the biological activities of these potent substances can be expressed at the level of the enzymes responsible for their biosynthesis and degradation. At present little is known about the enzymes involved in the termination of their biological activity and even less is known about the enzymes involved in their biosynthesis.

The control of neuropeptide activity by specific peptidases both to regulate production of active fragments from larger precursors and to specifically degrade the active products is an important central issue in neuropeptide function. A promising line of investigation of this phenomenon is proposed for purification of cation-sensitive neutral endopeptidase and partial purification of prolyl endopeptidase. Both enzymes have been characterized in terms of molecular weight, cation sensitivity, pH optimum, sensitivity to inhibitors, regional brain distribution, and peptide bond specificities. Even at this rather early stage of the work, several possibilities of specific biological functions of these enzymes have been suggested. Neutral endopeptidase is enkephalinogenic when tested on alpha-endorphin. Prolyl peptidase cleaves substance P specifically at the single peptide bond that generates two active fragments (C-terminus is much more potently bound to synaptic membranes than sub-P itself; N-terminus is a neurite growth factor). The facts that angiotensin converting enzyme and prolyl endopeptidase have some overlapping specificity and that angiotensin converting enzyme inhibitors given to rats increase brain levels of substance P may indicate the prolyl endopeptidase does function physiologically to control levels of this hormone. The studies designed to produce specific endopeptidase inhibitors using peptide aldehydes may provide both a useful probe of the physiological function of these enzymes and a new class of neuroactive drugs.

Another study is concerned with the investigation of conversion and inactivation of peptide hormones. Two separate series of experiment are planned: (1) those concerned with enzymes involved in conversion as defined by the production of smaller fragments from precursor materials; and, (2) enzymes involved in the breakdown and inactivation of active peptides. Several systems will be studied. In the first, angiotensin(s) will be studied with respect to the two enzymes involved in conversion, namely, renin and the angiotensin-1 converting enzyme. The second group of polypeptides are the lipotropins. The enzymes involved in the cleavage of beta-lipotropin to its individual fragments will be investigated. Other experiments will invetigate the inactivation of LHRH where considerable progress for purification of inactivating enzyme has been achieved. Other studies of a similar type are being conducted with somatostatin and the opioid peptides. Data obtained will be useful for basic knowledge on the formation and metabolism of brain hormones, and for developing analogs with higher potency and longer action which may be important in clinical implication.

Clinical Manifestations of Neuropeptides

Parkinson's Disease

The idea that a specific neurotransmitter deficiency is important in the pathophysiology and clinical manifestations of a neuronal-system degeneration has been developed in Parkinson's disese and Huntington's chorea. Both disorders have specific clinical and neuropathologic features. Their pathogeneses are different, since Parkinson's disease is usually sporadic, whereas Huntington's disease is an autosomal-dominant disorder with a complete degree of penetrance.

The documented loss of dopaminergic cells in the substantia nigra in Parkinson's disease appears to acount for most of the clinical manifestations, including slowness of movement, rigidity, and tremor, and also for its successful, though temporary, alleviation with L-dopa. However, the recognition of the loss of nigral dopaminergic cells has not provided any clues to the fundamental nature of this degenerative process. Hypothalamic dopaminergic neurons are largely preserved in this disorder, as is their neuroendocrine function, so that a generalized dopaminergic cellular disorder does not appear to occur. Undefined additional factors must contribute to the selectivity of the degenerative process. Several peptides, including somatostatin, substance P, cholecystokinin (CCK), and the enkephalins, are present in high concentration in the basal ganglia. Immunocytochemical studies and measurement of peptide changes in Parkinson's disease may contribute to a further definition of the disorder and possibly to a clarification of its pathogenesis.

Huntington's Disease

Huntington's disease affects other neuronal populations; cellular loss is most extensive in the putamen and caudate nucleus and less widespread in the lower laminae of the cerebral cortex. Other areas of the basal ganglia are less severely affected. There is no explanation for this pattern of cell death. The cellular loss in the putamen and caudate is accompanied by a loss of the neurotransmitter gamma-aminobutyric acid (GABA) and of glutamic acid decarboxylase, its synthesizing enzyme. However, it is clear that the deficiency of this neurotransmitter is not itself the cause of cell death.

The neuronal loss in Huntington's disease is also accompanied by changes in the regional content of acetylcholine and certain peptides. The concentration of substance P is decreased in the globus pallidus and the putamen. Levels of CCK and met-enkephalin are reported to be decreased in the basal ganglia in Huntington's disease, whereas levels of vasoactive intestinal peptide (VIP) are normal. Concentrations of somatostatin are considerably increased in the caudate, putamen, and globus pallidus. Also, increase in thyrotropin-releasing hormone (TRH) in tissue at autopsy of patients with Huntington's disease has been found. These findings point to a degree of neuronal selectivity in the degenerative process.

Pain

The neurotransmitters that relay nociception have been extensively investigated and recent experiments have implicated several peptides, notably substance P. The evidence that substance P is a primary sensory neurotransmitter is convincing. The substance is released from the spinal cord after depolarization by potassium or electrical stimulation. Peripheral nerve stimulation of nociceptive fibers elicits release of the peptide into the CSF.

Microiontophoretic application of substance P results in prolonged excitation of dorsal-horn neurons, which can also be shown to be activated by noxious peripheral stimuli.

Peptides also function in pain pathways at other sites in the CNS. In the early 1970's it was shown that electrical stimulation of discrete areas of the brain stem, esecially the ventrolateral periaqueductal gray (PAG) matter of the midbrain, produces analgesia in animals and human beings. The presence of opioid receptors has been documented in similar brain regions. Considerable overlap is found between the sites of stimulation-produced analgesia and of analgesia induced by intracerebral opiate injection; the PAG is the most effective site for both. These data suggest that endogenous opioids may be active in this system. In addition to high receptor concentration in the PAG, immunohistochemical studies show a rich field of enkephalin terminations. Further evidence that opioid peptides are involved in the pain relay at this level is the finding that analgesia produced by PAG stimulation in human beings is partially blocked by naloxone and is associated with a rise in beta-endorphin. Intraventricular administration of beta-endorphin is effective in causing analgesia in laboratory animals, whereas the intravenous route is not, presumably because of failure to cross the blood-brain barrier. Intrathecal injection of beta-endorphin in human beings is effective in causing profound analgesia.

Analgesia can be induced by agents that cause depletion of substance P. Capsaicin, a substance that is obtained from red pepper and has been shown to be structurally related to homovanillic acid, causes release and nerve terminal depletion of substance P from the spinal cord, accompanied by elevated peripheral thresholds to painful stimuli. Long term administration of capsaicin leads to degeneration of small diameter sensory neurons that contain substance P, and the concentration of the peptide in the spinal cord is reduced by 50 per cent. These observations provide evidence for a function of the peptide in pain transmission at the spinal cord level. An interaction of substance P with enkephalins at the spinal-cord level is suggested by evidence that enkephalins inhibit release of substance P from sensory neurons in culture.

Behavioral Responses to Neuropeptides

Learning and Memory

Research on the neurochemical basis of learning and memory has been one of the major concerns in the neurosciences. The theoretical implications of the functions of brain peptides in higher processes of the central nervous system is of considerable interest. Clinical implications of research on neurochemistry of learning and memory are appreciated when it is realized that there is no adequate therapy for memory derangements found in clinical neurology and geriatrics.

Vasopressin (VP), a neurohypophyseal hormone, has been implicated in memory processes of the CNS both in humans and in rats. A large body of data implicates VP in memory processes for active and passive shock-avoidance tasks. Oxytocin (OT), another neurohypophyseal hormone, has been shown to have effects opposite to those of VP on avoidance behavior in normal animals. Indeed, it has been suggested that OT is an endogenous "amnesic peptide". The alleged effects of VP on memory processes in normal rats may be unrelated to its endocrine actions because a VP analog, desglyeinamide-lysine-8-vasopressin which has minor antidiuretic, pressor and adrenocorticotropin (ACTH) releasing activities, has effects on avoidance behavior similar to those of VP.

Discovery of the Brattleboro strain of rats (HODI) which exhibits congenital hypothalamic diabetes insipidus allowed another possible test of the hypothesis that VP is involved in CNS processes. These rats lack VP in the brain. These rats are also inferior in acquiring and maintaining active and passive shock-avoidance behavior when compared with normal heterozygous DI rats. The behavioral differences could be obliterated by injections of VP into HODI rats. Studies have found that HODI rats actually show better retention of the aversive component in an approach-avoidance behavioral task than normal animals. The interpretation, based on data gathered on HODI rats, that VP is involved in memory needs a more complete characterization than is presently available.

Feeding Behavior

The central nervous system is known to play an important role in body weight regulation through its control of behavioral, hormonal, and metabolic events. Recent studies in animals have implicated several peptides in the regulation of feeding behavior. CCK, TRH, and insulin are reported to be satiety factors, decreasing food intake, whereas beta-endorphin has been implicated in states of increased food ingestion. The site of action of these peptides in affecting feeding behavior has been presumed to be within the CNS, with controversy over whether this effect is mediated through the ventromedial hypothalamus; interaction with the noradrenergic system has been proposed. Suppression of feeding by CCK has also been reported to be mediated through a parenteral abdominal site.

Another line of investigation suggests that central monoamine system controls the body weight regulation. These studies are based upon an animal model. In genetically obese mice in which abnormalities have been uncovered in catecholaminergic system, the relationship of spontaneously occuring obesity to monoamine function is being investigated. In the diabetes mouse, reduction of central norepinephrine levels improves the obesity syndrome. Experiments are being conducted to explain this phenomenon. And, the question of the effector mechanisms in the central control of body weight regulation is being examined. In the most widely studied models of abnormal weight regulation, rats with either ventromedial or lateral hypothalamic lesions, altered autonomic function is apparent. Data are accumulating to suggest that a change in the sympathetic nervous system may be important in weight changes that follow the lesions. These studies will examine the contribution of central catecholamines to disturbances in autonomic function related to feeding and body weight.

Cholecystokinin (CCK) peptides are present in brain in high concentrations, and CCK and its specific receptors have been shown to be localized in such areas as cortex and hypothalamus. Recent evidence strongly suggests a role for brain CCK in the control of feeding behavior. CCK, when injected into the cerebral ventricles of sheep, acts as a highly potent agent in suppressing feeding behavior. Of real physiological significance is the finding that satiety can be blocked by injection of CCK antiserum into the CSF. It is hypothesized that CCK is released in the brain during feeding, possibley secreted into the ventricular system and transported via CSF, and acts on CNS receptors involved in the elicitation of satiety. Investigations are being conducted that will determine rates of release of CCK into CSF during hunger and satiety and determine sites of release as well as sites of action of brain CCK in causing satiety. Thus, these experiments will provide additional information necessary to establish the physiological role of CCK in brain in the control of feeding behavior.

In another study the neuroanatomical organization of areas of the nervous system are being traced which are responsible for the control of food intake and body weight regulation. Although it has been known for some time that damage to certain areas of the hypothalamus can lead to obesity in an otherwise normal experimental animal. The neuroanatomical organization of these areas, which include the ventromedial (VMN), arcuate (ARC) and dorsal premammillary (DP) nuclei, is not well understood. Recent biochemical evidence based on chemical stimulation and measurement of catecholamine levels has also implicated the paraventricular nucleus (PVN) and the median eminence (ME). The present series of experiments are aimed at 1) elucidation of hypothalamic organization in normal rats and 2) determination of possible anatomical and biochemical abnormalities in the brains of genetically obese rats. Normal cytoarchitectonic features as well as neural connections of VMN, ARC, DP, PVN and ME will be studied. In humans a relationship exists between obesity and certain diseases. Elucidation of the neuroanatomical pathways involved in the control of food intake and body weight regulation as well as demonstration of abnormalities in the brains of genetically obese animals may be of use in therapeutic approaches to obesity.

Temperature Regulation

Temperature regulation represents a complex interplay of several causative agents and/or pathological conditions. Circadian temperature cycle may occur as a result of hypothalamic injury (tumors, cysts, etc), imbalance of neuropeptides in the brain affecting thermoregulatory system, transport of pyrogens in cessation or induction of fever, hormones and neurotransmiter release, calcium/sodium imbalance in the hypothalamus, etc.

Hypothalamic lesions produce devastating effects in man. Many of these lesions are caused by tumors or cysts arising from tissue at the base of the brain or the floor of the cranial vault and can be successfully treated if detected in time. The classic signs of hypothalamic injury are useful in making the diagnosis, but many of them occur late in the history of the injury. In the course of these studies on fever mechanisms in patients and subhuman primates, with neurological injury, the hypothesis was developed that the disruption of the circadian temperature cycle may be a useful diagnostic sign of hypothalamic dysfunction. The plan is proposed to test this idea by observing circadian temperature cycles in monkeys in which hypothalamic lesions are progressively produced, as an analogue of the progressive injury that occurs in man. Temperature cycles will be recorded in patients with known or suspected hypothalamic injury to correlate the temperature cycles with evidence of central lesions. Information from these studies may be useful in the diagnosis of hypothalamic disorders.

Previous research on this project has shown that the study of clinical cases of dysthermia can provide information that is directly useful to the clinician, and it can serve as a guide to important research problems. Patients are being studied to learn whether, as described above, circadian temperature cycles are altered by hypothalamic lesions. Also other patients have been tested with CNS sarcoid disease, Wernicke's encephalopathy, Frohlich's syndrome, fever of unknown origin, accidental hypothermia, heatstroke, drug fever, and CNS disorders due to perinatal anoxia. These studies may provide a great deal of return in terms of direct applicability of the data to health sciences, and clinical application.

Neuropeptides: From recent research on central peptides it has become clear that many of them may participate in the control of physiological functions. Data collected indicate that several peptides alter body temperature when given centrally, a finding which raises the possibility that these substances normally act within neuronal pathways which control thermoregulatory processes. Several screening tests indicate that at least 5 of the 16 peptides tested so far may have roles in central temperature control. Two of the peptides have been found to be antipyretic and may normally serve to limit the amplitude and duration of fever; the other three cause body temperature to rise and may be central mediators of fever of hyperthermia. At least one of the antipyretic peptides, ACTH, is known to be released during fever in man. The vast potential for understanding the role of central peptides in thermoregulatory phenomena, and the possibility that this understanding may allow effective control of clinical fever and dysthermias, suggest that intensive investigation of the effect of these naturally occurring substances should have a high priority. Further insights into the role of these peptides in thermoregulation, combined with existing knowledge of their roles in other physiological functions, might explain a number of mysterious interactions such as the characteristic cycling of body temperature that is coupled with the female reproductive cycle and the normal circadian changes in temperature.

Pineal Gland: Among the numerous experimental demonstrations which purport to reveal a pineal function, only a few stand out as well-defined and reasonably unambiguous. Pineal organs are commonly perceived as components in systems subserving reproductive and diurnal rhythmic functions. It has, however, been widely appreciated that pineal organs are intimately involved in other roles, including thermoregulation and thermal adaptations. Indeed, a thermal association of pineal organs has been confirmed in more vertebrate classes than for the two other ascribed roles. In spite of this, it is quite safe to say that little is known about the role of the pineal gland in thermoregulation per se. The gland has been implicated as a modulator of other organs and through this role may be acting as a "pressure valve" of physiological responses during exposure to stress.

Previous studies have suggested both increased activity by the pineal gland during temperature stress and decreased thermal tolerance by animals after removal of the gland. In view of the promising leads suggested by the limited literature, surprisingly few studies have been specifically directed at determining the role(s) of the pineal gland in thermal stress. The ambiguity concerning the involvement of the pineal gland in thermoregulation is largely a result of testing animals within the non-stressful confines of their thermal neurtral zone. The experiments designed pay particular attention to the involvement of the pineal gland in thermoregulatory responses at temperatures both above and below the animal's thermal neutral zone to identify the mechanisms by which the pineal gland may influence physiological processes of heat generation within the body and heat exchange with the enviroment.

HEREDITARY LIPID STORAGE DISEASES AND OTHER METABOLIC DISORDERS

In this section there are at present 70 projects, of these about 35 are directed towards inherited metabolic disorders. The program supports fundamental as well as clinical research on lipid storage and other inherited diseases. Some of the diseases being investigated are Nieman-Pick, Gaucher's, Krabbe's, Fabry's, Metachromatic leukodystrophy, Mannosidosis, I-Cell Disease, Batten disease, Adrenloeukodystrophy, and Gangliosidoses (e.g., GM1, GM2, GM3). Also included in this program are related areas pertaining to myelin, cholesterol, phospholipids, keto and hydroxy fatty acid metabolism. Other projects deal with amino acid imbalances and brain metabolism, neurotransmitter metabolism, vitamin deficiencies, etc.

Lysosomal lipid storage diseases have emerged as a cohesive group of inborn human disorders of metabolism. They all share some common characteristecs, such as recessive genetic traits, biochemical profiles of accumulated lipid material, distortion of morphological features and lysosomal enzymatic defects. Most of these diseases have progressive nervous system deterioration as their major component. Onset of neurological signs in these disorders range from infancy to adult life, and all are severely disabling or fatal diseases. Data on population genetics and incidence are fragmentary due to the recent discovery of most of these diseases and because the biochemical methodology needed to differentiate between clinical subtypes has only become available within the past few years. The insidious nature of the pattern of recessive inheritance permits the carrier genotype to become widespread in a population in significant numbers. Screening for the carrier state and prenatal diagnosis provide potential parents with needed information.

Although progress in enzyme replacement therapy has been significant, the optimistic goals of effective therapy for human lysosomal storage diseases have not yet been realized. There are several hurdles to be surmounted before such a therapy can become a reality. These include: protection of replaced enzyme against bioinactivation and immunological reactivity, perfection of methods for delivery of needed enzymes to target sites, availability of natural substrates to test the missing enzymes in vitro, and availability of animal models replicating these diseases for testing therapeutic strategies. Once an affected child is born with any one of these diseases, there is at present very little to offer to restore him to a normal and productive state. Some alternative methods need to be explored. These include safe and effective means to penetrate the blood-brain barrier for delivery of missing enzyme, use of external agents to activate dormant enzymes, production of endogenous stimulators, such as peptides, to complement or replace the missing enzyme, and use of internal or external inhibitors to slow down the enzyme activity which produces the accumulated metabolites.

As stated above, treatment of individuals with most inherited diseases has so far been palliative only. The long range thrust of research in the area should be directed toward corrective therapeutic strategies. An ideal cure for inherited disorders would be substitution of normal DNA coding for synthesis of the defective gene product. While current theoretical concepts and the potentials for gene therapy do offer hope in the future, progress in gene therapy will be slow because of technological and ethical considerations. The Neurological Disorders Program takes a long range view in encouraging research in these and other promising approaches.

Common Characteristics of Storage Diseases

Genetics

One of the common features of these storage diseases is that they all are hereditary. With the exception of Fabry's disease (and possibly adrenoleukodystrophy and Menkes' disease which are not strictly lipid storage diseases), all are transmitted as autosomal recessive defects. Statistically, law of Mendelian inheritance is followed. Two heterozygotes individuals will produce one normal, 2 heterozygotes and one affected child. This observation is supported by the fact that in the heterozygotes the defect, as determined by enzymatic activities, falls in-between the values of normals and those of affected offsprings. Heterozygotes, even with 50% of genetic defect, lead normal lives.

Fabry's disease, on the other hand, is transmitted as a recessive characteristic by the X-chromosome. This means that only the mother need be a carrier to have an affected (in this case hemizygous) male child since males have only 1 X-chromosome. Half of the carrier's sons will have the disorder, half will not be involved. Fifty percent of her daughters will be heterozygotes. The clinical picture amd inheritance patterm of Fabry's disease is a little more complicated than other lipid disorders since some of the female heterozygotes have manifestations of the disease although usually of much less severity.

Detection of heterozygotes

Clinical detection of carrier state can be made by measuring the levels of enzyme activities of leukocytes from venous blood. The test is reliable and provides a convenient procedure for estimating the rate of progress of the disease, because the determination carried out with white cells accurately reflects the level of enzyme activities in all body tissues. Similar reliable tests can be made using cultured skin fibroblasts. These fibroblasts can be stored at liquid nitrogen temperature, thawed, and can be regrown in tissue culture medium still retaining all the characteristic features of parent-cell line. Use of leukocytes and fibroblasts have obviated the necessity of diagnostic procedures involving organ biopsies. There are, however, a few exceptions where the correct diagnosis cannot be established using intact fibroblasts or leukocytes, e.g., in I-Cell disease and in Batten disease.

Genetic Counseling

The combination of amniocentesis, the ability to grow fetal cells in tissue culture, and knowledge of the specific enzymic defects in lipid storage diseases has provided genetic counselors with the ability to diagnose these storage diseases in the second trimester of pregnancy. The feasibility of these procedures has been demonstrated repeatedly. For example, using a method for the prenatal diagnosis of such diseases by amniocentesis and enzyme assay, over thousands of individuals throughout the United States, and other nations have been tested for their carrier status.

Biochemistry

The main core of nearly all accumulated lipids in the storage diseases is called ceramide. Ceramide is composed of mainly three components; two long chain saturated fatty acids joined through an amino acid-serine. The first product is sphingosine. It is a long chain amino alcohol synthesized in all of the body tissues by the combination of two simple precursors, palmitic acid (C16) and serine. The second step in the formation of ceramide is an addition of another long chain saturated fatty acid usually stearic acid (C18) attached to the nitrogen atom of carbon 2 of sphingosine. The terminal -OH group of ceramide can be substituted with a variety of compounds to form different sphingolipids. For example, in Niemann-Pick disease, lipid that accumulates is ceramide attached to phosphorylcholine. This is called sphingomyelin which can be defined as ceramide-phosphoryl-choline. The

defective enzyme is sphingomyelinase which is unable to cleave the terminal phosphorylcholine moiety.

Cerebroside is a generic term for monohexosylceramide, i.e., the -OH group of ceremide is substituted by a sugar hexose such as galactocerebroside, glucocerebroside found in Krabbe's disease and Gaucher's disease respectively. Sulfatide is galactocerebroside with an additional sulfate group attached to galactose found in metachromatic leukodystrophy.

Ceramide oligohexosides are sphingolipids in which a series of hexoses are linked together. Unlike cerebrosides, all ceramide oligohexosides in the brain have a glucose moiety linked to ceramide. For example, in Fabry's disease the accumulated compound is ceramide-glucose-galactose-galactose (ceramide trihexoside)

Gangliosides are defined as sphingolipids that contain sialic acid. Sialic acid is a generic name for N-acylneuraminic acid, and the acyl group of sialic acid in gangliosides of brain is always in acetyl form, N-acetylneuraminic acid and is abbreviated as NANA. There are over 12 kinds of gangliosides that have been identified in the brain. All have ceramide oligohexosides as the backbone with one or more NANA moieties attached. Out of all the gangliosides, GM1, GM2, GM3 and their asialo forms have been investigated intesively.

Morphological Features

While much is known about the biochemistry of these storage diseases, knowledge about the morphological basis, as to how the lipids accumulated lead to neuronal dysfunction, is woefully lacking. It is surmised that the substances accumulated may be cytotoxic. For example, in Krabbe's disease the hypothetical presence of psychosine is implicated in the selective loss of oligodendroglia. Unfortunately, no direct evidence is available that psychosine or other accumulated stored lipids lead to neuronal alteration resulting in neuronal dysfunction.

Recently, studies have been conducted on the tissues from several different forms of human gangliosidoses in an attempt to identify abnormalities from the standpoint of neuronal geometry. The studies showed the presence of new 'dendritic-like' structures covered with many spines between the cell body and initial axonal segment of pyramidal neurons. Electron microscopic examination of the surface features of these large neuronal processes, designated "meganeurites" showed that the spines are postsynaptic components of morphologically identifiable synapses. In classical Tay-Sach's disease (infantile GM2-gangliosidosis) meganeurites of extraordinary shape were found in virtually all pyramidal neurons revealed by the Golgi method. It is proposed that meganeurites and meganeurite synapses may contribute to the onset and progression of neuronal dysfunction in storage diseases by altering electrical properties of the neuron and modifying integrative operation of somadendritic synaptic inputs.

Metabolites Accumulated

In each storage disease a specific lipid or a class of related lipids has been shown to be accumulated in nearly all the body organs and in blood and enzymes responsible for their terminal degradation are either absent or inoperative. However, in Krabbe's disease the accumulation of galactocerebroside has not been demonstrated, even though galactocerebrosidase is absent. Similarly, in Gaucher's disease, only spleen, lymph nodes and bone marrow show accumulation of glucocerebroside; CNS involvement has not been implicated.

Enzymatic Abnormalities

Each storage disease is characterized by a specific defective enzyme which is unable to cleave the terminal moiety of stored lipid. That means that the synthetic processes involved in the synthesis of stored compounds are normal, it is the terminal degradative process which is impaired. There are, however, a certain exceptions to this general statement. For example, in the I-Cell disease, absence of two enzymes is suggested; beta-galactosidase and alpha-fucosiadase. Similarly, in adrenoleukodystrophy evidence of two-disease entity has been presented. Also multiple sulfatase deficiency in metachromatic leukodystrophy has been observed.

Enzyme Replacement Therapy

The theoretical possibility of correcting inherited lysosomal diseases by enzyme replacement was recognized soon after the pathogenetic basis for these diseases was first advanced. During the past decade significant progress has been made toward this worthy goal. For example, patients with Tay-Sachs, Fabry's and Gaucher's diseases were injected with enzyme purified from human urine or placenta.

Most of the exogenous enzyme administered to an infant with GM2 gangliosidosis was concentrated in the liver but was not found in brain or cerebrospinal fluid. A precipitous reduction (50%) in plasma globoside occurred 4 hours post-infusion. Other plasma sphingolipids rose to levels above pre-injection values. There appeared to be a 2.4 fold increase in liver hexosaminidase above that which could be accounted for by exogenous enzyme activity, suggesting possible mutant enzyme activation. The patient's neurological disease was not apparently altered.

Patients with Fabry's disease were infused with exogenous ceramidetrihexosidase with resulting reduction in serum ceramidetrihexoside to normal levels. Evidence is presented to support the conclusion that hydrolysis of this substrate occurred at an extra-circulatory site, probably within lysosomes.

Patients with adult Gaucher's disease were infused with exogenous glucocerebrosidase, with resulting decrease of levels of glucocerebroside in liver and erythrocytes.

In addition to the examples cited above, several trials involving human patients and experimental animals with other storage diseases have also been undertaken. Although, in practice the technique of detecting these disorders in early stages with fibroblasts has been fully established, the clinical application of enzyme replacement therapy in diseased subjects is far from perfect. It has been observed that the injected enzyme is readily metabolized in the liver and very little, if any, reaches the brain. Thus, the major problem in enzyme replacement therapy in lipidoses is the existence of blood-brain barrier.

Blood-Brain Barrier

The blood-brain barrier in vertebrates is thought to be created by the specialized structure of the capillary-glial complex. There are two components to the blood brain barrier: 1) a passive component, which acts as a physical barrier and consists of endothelial cells which are sealed by tight junctions and which contain few intracellular vesicles capable of transporting material from blood to brain; and 2) an active component which is responsible for selective permeability and which is composed of the enzyme systems of endothelial and adjacent astrocytes which acts to facilitate transfer of substances in one or both directions. This component has many characteristics of transporting epithelia.

A number of experimental treatments, including mechanical trauma, thermal lesions, embolism, hypercapnic hypoxia, enzymatic disturbances, hyperosmotic solutions, extreme stress, radiation, electric shock, infection, intoxication, acute hypertension, hyperbaric oxygenation, urea and other solutes, can lower the blood-brain barrier with localized fluid and proteins into the intracellular spaces of the brain parenchyma. The great majority of these procedures, although useful in studying various physiopathological aspects of the blood-brain barrier, do not offer immediate possibilities of clinical application.

Recently, emphasis has been placed in devising methods of enzyme delivery to the target cells which offer some potential for circumventing the impediments offered by the blood-brain barrier. These methods take into account the stability of enzyme in extracellular fluids and lysosomes and the efficiency of enzyme uptake by target and other cells. This form of therapy requires that in addition to being efficacious in amelioration of lysosomal disease, the treatment must not complicate the primary disease and should not induce secondary complication.

Enzyme encapsulation

Recently, a few reports have appeared which provide encouraging evidence that encapsulation of enzyme in lipid vesicles (liposomes) may overcome many of the difficulties encountered in perfecting enzyme replacement therapy. Liposomes consist of lipid bilayers alternating with aqueous compartments, arranged in closed concentric spheres. Since these artificial liposomes are composed of lipid and aqueous layers, they have both hydrophilic and lipophilic properties and as such can entrap water soluble as well as lipid soluble compounds. Using this technology the feasibility of administering enzyme (beta-galactosidase) in GM1 cats has been tried.

Preliminary results indicated that liposomes are non-toxic when administered intravenuously. Encapsulated B-galactosidase remained stable in liposomes for a period greatly exceeding that of naked enzyme. Liposomes were concentrated in several organs (including brain?). Uptake of liposomes by feline leukocytes and skin fibroblasts greatly exceeded that of naked enzyme. Although the results seem encouraging, direct delivery of intact enzymes to brain cells by this method seems a remote possibility. It is however, possible to deliver smaller peptides or other activaors of reasonably smaller molecular weight which may pass through blood-brain barrier to activate a dormant or mutant enzvme in the brain.

Activators and inhibitors

As indicated above, the enzyme replacement therapy as such offers at present only a remote possibility for controlling lysosomal storage diseases. Use of activators or helper protein which can cross blood-brain barrier may be the next logical step to be followed. This approach has been tried in Krabbe's and Gaucher's disease. Several compounds structurally related to galactocerebroside or ceramide have been synthesized. One group of homologous compounds particularly N-decanoyl-2-amino-methylpropanol acted to stimulate the galactosidase in rat brain. As much as 62% stimulation could be achieved in vitro, presumably by combination of the amide with some sensitive site on the enzyme molecule. A test with brain from a child who had died of Krabbe's disease showed that the activator worked with this enzyme too, as well as with the normal human enzyme. This finding raises the possibility that Krabbe's disease could be treated by administration of an appropriate, more effective enzyme stimulator.

Use of inhibitors in blocking or slowing down the synthesis of cerebrosides has equally good potentialities for treating these storage diseases. A series of inhibitors for glucosyltransferase, the enzyme that synthesizes cerebroside from ceramide, has been developed. All contain a ketone or epoxy group that apparently binds covalently with the enzyme thus blocking or slowing down cerebroside synthesis. These compounds are being tested in animals.

Some tests with potential inhibitors showed good activity with N-decanoyl-3-phenylamine-3-propanol. It acts noncompetitively, persumably at some sensitive site. In culture media with fibroblasts from Gaucher's patients, it produced normal appearing cells, presumably by slowing the rate of glucocerebroside accumulation. Thus this compound may have a potential value in the treatment of patients with Gaucher's disease.

Specific enzyme inhibitors may also be useful in producing an animal model for specific storage disease. For example, conduritol-beta-epoxide when injected into mice, caused no appreciable increase of glucocerebroside in spleen and in liver, but caused 3-4 fold elevation in the brain. At the same time glucocerebrosidase was inhibited. The enzyne activity at 5 hours was found to be almost zero in four organs, but returned gradually to almost a normal level in 16 days.

In addition to these synthetic stimulators or inhibitors, a naturally occurring activator has been purified from human liver. It is a glycoprotein. The physical properties of the activator are: heat-stable, nondialyzable; molecular weight about 21,000; isoelectric point (pI), 4.1. The purified activator stimulates the hydrolysis of GM1 by B-galactosidase, GM2 by B-hexosaminidase as well as ceramide trihexoside by alpha-galactosidase A or B. The hydrolysis of sphingoglycolipids by glycosidases depends upon the amount of activator added. An antibody against the activator was developed from rabbits. The specificity of the antibody to the activator has been established.

Batten's Disease

Neuronal Ceroid-Lipofuscinosis (NCL)

Batten's disease is a genetically determined group of disorders characterized by seizures, visual loss and progressive mental impairment. Motor disorders consisting of spastic weakness, rigidity combined with athetosis or dystonia, and ataxia invariably appear as the disease progresses. Death usually occurs from the complications of the bedridden vegetative state of the patient in the end-stages of the disease. The disease may progress rapidly to death within one year following onset or pursue a more prolonged course over several years.

The specific familial cerebral degeneration associated with Batten's Disease was originally linked to other forms of "familial amaurotic idiocy," particularly the ganglioside storage diseases. This association arose because of the presence of storage material in the brain and retina in both the gangliosidoses and Batten's disease.

Based upon the biochemical composition of the material accumulated and the neurological manifestations, lipid storage diseases can be divided into two main groups of inherited diseases.

1) Diseases Related to Ceramide Metabolism: This group is characterized by the accumulation of lipid material known as ceramide and its substituted products such as sphingomyelin, hexose-cerbrosides, and gangliosides. These diseases are collectively referred to as lysosomal storage diseases, inborn errors of lipid metabolism, sphingolipidoses, or gangliosidoses. In each of these diseases a specific lysosomal hydrolytic enzyme has been identified as either deficient or absent. These enzymes are responsible for degrading the stored lipid material; as deficiencies lead to accumulation of such material resulting in neuronal dysfunction and disease states.

2) Diseases Related to Storage of Lipopigments: A second group, collectively known as Batten's disease or Neuronal ceroidlipofuscinoses (NCL) is characterized by the accumulation of autofluorescent lipopigments in neuronal and extra neuronal tissues. In this group of diseases, the sphingolipid profiles are normal but a group of enzymes known as peroxidases, which prevent oxidation of certain metabolites seems to be defective. The accumulation of autofluorescent lipopigments may be due to an increased rate of peroxidation of polyunsaturated fatty acids; presumably related to the markedly reduced activity of a p-phenylenediamine (PPD)-mediated peroxidase. The same PPD-mediated peroxidase has been found to be deficient in all the three types of Batten's disease.

Clinical Variants of Batten's Disease

The following classification is based on the age of onset and the severity of disease.

Late Infantile, the Acute Jansky-Bielschowsky Type: This is the most severe form and is a rapidly progressive disorder having an early onset. Generalized convulsions leading to coma and finally to death between age 2 and 6 years are observed in this form. Another infantile type of neuronal ceroid-lipofuscinosis called Finnish type has also been reported.

Juvenile, the Chronic Spielmeyer-Sjogren Type: This is a slowly progressive form beginning with the generalized convulsion of relatively late manifestations. The course may last up to 20 years with an average duration of 11 years.

Adult Form, Kuf's Type: This is a relatively milder form and begins during adulthood and is usually not associated with blindness. The disorder produces less severe mental disturbances then the infantile form.

Diagnosis

The diagnosis of NCL and its variants is dependent upon the demonstration of the autofluorescent pigments, ceroid and lipofuscin, in the brain and other organs by special staining and autofluorescent techniques. Morphologial studies distinguish between the infantile and juvenile types of NCL. Neuronal tissues from patients with late infantile form of Jansky-Bielschowsky syndrome contain predominantly curvilinear bodies, as demonstrated by electron miscroscopy. Granules with an internal structure reminiscent of finger prints are said to be indicative of juvenile amaurotic idiocy or Spielmeyer-Sjogren syndrome.

Recently, an improved procedure for the solubilization of peroxidase from leukocytes by combining the freeze-thawing and sonication has been developed. Using this preparation with p-phenylenediamine-O-dianisidine and guaiacol as hydrogen donors, the leukocytes of NCL patients were found to be deficient in peroxidase activity. Using another agent, nitro-blue tetrazolium (NBT), reduction values in the leukocytes of the patient were also found to be significantly higher than normal controls, indicating the impairment in the hydrogen peroxide catabolism. The determination of NBT and leukocytes peroxidase may also serve as a diagnostic test for NCL disease.

Treatment

Experimental Animal

In order to test the hypothesis that Batten's disease may be associated with an increased rate of unsaturated fatty acid peroxidation, dogs, English Setters with this genetic disease were a fed controlled diet containing antioxidant drug. These trials revealed that vitamin E in daily doses of 400 mg. per day at the age of 7 months or earlier delayed the onset of the disease by approximately 2-3 months, however, this treatment did not improve the life span. Also vitamin C given with the onset of symptoms was ineffective. If the treatment is initiated at the earliest age, it is possible to produce 100% homozygous affected offsprings by mating affected animals which had been pretreated with vitamin C.

Human NCL Patients

Treatment of human patients consisted of daily doses of 2 gm vitamin E., 0.5 gm vitamin C., 200 mg santoquin as antioxidant and 1 gm DL methionine. Patients with the Spielmyer-Sjogren type of NCL have been treated with this regimen. This treatment showed little effect in patients who had fully developed disease, except that it did make the patient more manageable. If started at the incipient or early stage of the disease, there is significant amelioration of the progressive mental deterioration and agitation. On the other hand, the retinal atrophy was not retarded in the patients whose treatment began at the initial stage of central visual disturbance.

Under treatment, EEG abnormalities are occasionally improved or at least do not deteriorate at the same rate as in untreated patients. Also, the intellectual performance was maintained at a stationary level for years, but visual deterioration was not retarded. It should be pointed out that others who have used this treatment have not been able to confirm these results.

Even though the treatment is moderately effective as a palliation, it is not curative and therefore not the final answer to the problem. Since peroxidase activity in rats can be increased by cyanocobalamine, this treatment has been added to the patients who already received the antioxidant treatment, however, the effect of this supplementation is difficult to assess because of the relatively slow progression of the natural disease. Under these circumstances therapeutic trials in experimental dogs and sheep which have already been used to a considerable extent will continue.

Biochemical Abnormalities

Para-Phenylenediamine (PPD) Mediated Peroxidase

It has been reported that a P-phenylenediamine-linked peroxiase is deficient in the granulocytes (leukocytes) of patients with Batten's disease, associated with early and excessive neuronal lipofuscin accumulation and with mental deterioration and blindness. A deficiency of the same peroxidase activity has also been found in the leukocytes of dogs with neuronal ceroid-lipofuscinosis. In addition, there was a deficiency of granulocyte myeloperoxidase, demonstrated histochemically with benzidine, which probably represents the same enzyme demonstrated with p-phenylenediamine. Normally, myeloperoxidase is present in the azurophil granules of neutrophilic polymorphonuclear leukocytes, and it is a lysosomal enzyme. Eosinophil granules also have peroxidase activity, but this appears to differ from myeloperoxidase and is believed to be a "true" peroxidase. Myeloperoxidase or PPD-linked peroxidase is reported to be similar to thyroid peroxidase biochemically found in Batten's disease. Although other workers have had some difficulty confirming the findings in Batten's disease, the fact that a deficiency of a P-phenylenediamine-linked peroxidase has also been detected in dogs with neuronal ceroid lipofuscinosis supports the suggestion that a defect in this peroxidase activity is related to Batten's disease.

Metabolites Accumulated

In the first decade of the 20th century, it was observed that lipid substances which accumulated in nerve cells represented a pigment. However, it was not until 1960 that the lipopigment nature of the ceroid deposits was conclusively proved. It was demonstrated that more than 50% constituent of these pigments was an acidic lipid polymer containing a fluorogen viewed as being a Schiff base derived from condensation of malonaldehyde with amino and amido groups. Therefore, the basic pathogenesis of NCL syndrome must center around the peroxidation of unsaturated fatty acids, a process that leads to the formation of malonaldialdehyde and other products. On the other hand, there is no accumulation of any one glycolipid or phospholipid. In fact, these complex lipids have concentrations smaller than those obtained from whole brain homogenates. The same applies to neutral lipids and fatty acids. Only one lipid is consistently increased in these pigments, namely lysobisphosphatidic acid, the nature of this increase remains unknown. It seems highly improbable that lysobisphosphatidic acid would represent the primary non-degradable compound leading to the accumulation of lipopigment.

Recently, evidence contrary to the one given above has been presented. Cystosomes filled with intensely fluorescent material in the form of curvilinear bodies have been isolated from the cerebral cortex of a 7 year old child who had died from late infantile form of Batten's disease. Forty three percent of material extracted suggested presence of retinoyl polyenes linked to a small peptide. The results indicated that the fluorescent component of neuronal storage material is a retinoyl complex and is not derived from peroxidized polyunsaturated fatty acid as has been previously thought. This finding has been disputed by some investigators.

Genetics

The acute Jansky-Bielschowsky and the chronic Spielmeyer-Sjogren type are both inherited as autosomal recessives and the Adult form (Kuf's Type) is inherited as an autosomal dominant. These diseases follow strictly Mendelian recessive inheritance characteristics. This statement is verified by the fact that the activities of heterozygotes have shown PPD-peroxidase activity values in between those of normal controls and of homozygous affected. The same Mendelian ratio has been observed in experimental animals, English Setters and South-Hampshire sheep.

Prenatal Detection of NCL

A simple assay for peroxidase activity in amniotic fluid is being developed. A narrow range of activity was defined between 17 weeks and term in normal human pregnanacies. From 30 weeks to term normal enzyme activity increased 40 fold. This increase is due primarily to the maturation of the fetal salivary gland. Though the opportunity to test this procedure has not arisen yet in human, it may prove useful in future studies where a human fetus is at risk. Presently experiments are planned to measure amniotic fluid peroxidase in animal model.

CONTRACT NARRATIVE

Neurological Disorders Program
October 1, 1980 - September 30, 1981
NO1-NS-9-2320

Title: Establishment of a Research Roster for Huntington's Disease Patients and Families.

Contractor's Project Director: P. Michael Conneally

Current Annual Level of Funding: $105,942

Objectives: To establish a national research roster of patients with Huntington's disease and their families. This roster will serve as a national source of information for physicians and scientists interested in locating Huntington's disease patients and families willing to participate in experimental studies into the diagnosis, etiology and treatment of this disease. Also to furnish statistical and demographic data on families collected.

Major Accomplishments: This contract has been in effect for about 21 months. Contractor has developed two questionnaires: A family history form for entering pedigrees and an in-depth questionnaire for affected individuals. A third data form is planned for those at risk.

Roster personnel have made an intense effort to contact families across the country. 305 separate families (comprising many individuals) have been entered, representing 36 states. 208 affected questionnaires have been received.

A brochure has been developed for distribution at scientific meetings. Notices in journals, booths at professional society meetings, and other forms of advertisement are being used to stimulate increased scientific utilization of the roster now that families are available. Issues of confidentiality have been sensitively handled and the response to the roster from scientists and families has been positive.

Proposed Course of the Contractor: This program is under the surveillance of an NINCDS project officer and performance is under continued review.

TAB 5.A -- EPILEPSY BRANCH -- EB/NDP

ANNUAL REPORT

October 1, 1980 through September 30, 1981

Epilepsy Branch, NDP

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

OVERVIEW 1-3

GRANT SUPPORTED RESEARCH 4

CONTRACT NARRATIVES

Absence Seizure Drug Studies and Long Term Followup of Patients with Absence Seizures 9
N01 NS 9-2196

Studies of Toxicology and Selected Pharmacology of Potential Anticonvulsants 10
N01 NS 0-2327

Epilepsy Information Transfer 12
N01 NS 0-2341

Comprehensive Epilepsy Program 13
N01 NS 6-2340
N01 NS 6-2341
N01 NS 0-2332

Treatment of Infantile Spasms 17
N01 NS 9-2321

Study of Experimental Anticonvulsant Drugs in Primates 18
N01 NS 1-2349

Investigation of Pharmacologic Posttraumatic Epilepsy Prophylaxis 20
N01 NS 2-2313

Publication of *Epilepsy Abstracts*, Volume 14 21
N01 NS 3-2303

Early Pharmacologic Evaluation of Anticonvulsant Drugs 22
N01 NS 0-2335

Table of Contents (cont'd)

RESEARCH PROJECTS

Development of Analytical Methods for Analysis of Potential Anticonvulsants 23
Z01 NS 02511-01 EB

Inhibition of Microsomal Primidone Metabolism by Phenytoin 25
Z01 NS 02512-01 EB

ANNUAL REPORT
October 1, 1980--September 30, 1981

Epilepsy Branch
Neurological Disorders Program
National Institute of Neurological and Communicative Disorders and Stroke
National Institutes of Health

The Epilepsy Branch is concerned with the prevention, diagnosis, and treatment of epilepsy. Direct, collaborative, and grant supported research programs have proven highly effective in support of its goals. Since its inception in 1966, the Epilepsy Advisory Committee has provided guidance to the program. This year, the Epilepsy Branch has made progress in several new areas. The Antiepileptic Drug Development Program, a key element of Branch activities, has been active in screening, toxicity evaluation, and initiating clinical evaluation of new drugs. The pharmacology laboratory of the Epilepsy Branch provides important support for the Drug Development Program. The Comprehensive Epilepsy Program supports the UCLA Comprehensive Epilepsy Program specifically designed to serve a minority population. Two Comprehensive Epilepsy Programs successfully made the transition from contract support to grant support: the University of Minnesota and the University of Washington.

In connection with data management from clinical trials, the Epilepsy Branch staff was augmented this year by Cheryl Seaman, R.N. and Yuko Palesch, M.S. An NINCDS Stride employee, Mary B. Fitzpatrick, completed an academic program with honors and continues as a full time employee in the information program of the Branch. As a participant in the WHO Neurosciences Research Program, the Institute's first Fellow, A. 'Kunle Bademosi, M.D., completed training and returned to Nigeria. He was followed by Qu Zhiping, M.D., a WHO Neurosciences Fellow from Shanghai who will spend one year with us. Following a period of service as Acting Chief, Neurosciences Branch, IRP, Susumu Sato, M.D. returned to the Epilepsy Branch to continue his activities in collaborative research.

The NINCDS Antiepileptic Drug Development Program has been especially effective in interesting pharmaceutical companies to pursue the development of new drugs for the treatment of seizures. The screening project received a record number of chemicals to determine possible anticonvulsant activity. These chemicals were evaluated by its contractor, the University of Utah. Ninety-day rat and dog toxicity studies began at Southern Research Institute under contract, and compounds from three firms have been evaluated there. In a major effort, Epilepsy Branch staff worked closely with the Contracting Officer, NINCDS, to develop a master agreement with task orders for clinical trials of antiepileptic drugs. This support mechanism will provide the opportunity to evaluate new drugs in any of the seizure classifications without the lengthy procedures normally associated with research contracts. A task order was awarded for the pharmacokinetic evaluation of progabide; two task orders for the clinical evaluation of this drug in complex partial seizures are planned for award in August 1981. This major undertaking in clinical evaluation of a new drug represents the reinstatement of the clinical thrust of the Antiepileptic Drug Development Program.

Meetings were held during the year with nine pharmaceutical companies regarding potential antiepileptic drugs in various stages of development. It is encouraging to note that a number of companies not previously associated with the marketing of antiepileptic drugs are now potential entries into this field. It is believed that support and advice from the Epilepsy Branch is a key element of their continuing interest in developing new agents for the treatment of seizures.

In 1972, a comprehensive volume, Antiepileptic Drugs, edited by D.M. Woodbury, J.K. Penry, and R.P. Schmidt, was published to provide an authoritative reference work as a single source on the recent advances and knowledge concerning antiepileptic drugs. Enough new information has been accumulated in the intervening years to justify a second edition, edited by D.M. Woodbury, J.K. Penry, and C.E. Pippenger, which is soon to be published. The Epilepsy Branch is prominently associated with this text: General Principles of Testing Antiepileptic Drugs in Humans--Clinical Considerations, by J.J. Cereghino and J.K. Penry; Clonazepam, by F.E. Dreifuss and S. Sato; Methsuximide and Phensuximide, by R.J. Porter and H.J. Kupferberg; Chemistry and Methods of Determination of Valproate, by H.J. Kupferberg; Mephenytoin and Ethotoin, by H.J. Kupferberg; General Principles of Testing of Antiepileptic Drugs in Humans--Statistical Considerations, by B.G. White; General Principles of Clinical Efficacy and Use of Antiepileptic Drugs, by J.K. Penry and R.J. Porter; Carbamazepine--Interactions with Other Drugs, by R. Levy and W. Pitlick; Carbamazepine--Relation of Plasma Concentration to Seizure Control, by J.J. Cereghino; and Potential Antiepileptic Drugs--Mexiletine, by J.J. Cereghino.

Significant contributions have also been made to the literature through the Raven Press publication, Genetics of Epilepsy: A Review, by M.E. Newmark and J.K. Penry. A review of the literature on catamenial epilepsy by M.E. Newmark and J.K. Penry was published (Epilepsia 21:281-300, 1980). Further evidence of the contributions of the staff in the field of antiepileptic drugs is the publication of Advances in Epileptology, XII Epilepsy International Symposium, edited by M. Dam, L. Gram, and J.K. Penry, published by Raven Press in 1981. This volume represents papers presented at the international meeting held in Copenhagen in 1980. Contributions are: New Drugs for the Treatment of Seizures: A Comprehensive Approach, by R.J. Porter, L.D. Smith, and H.J. Kupferberg; Carcinogenicity of Hydantoins: History, Data, Hypotheses, and Public Policy, by B. Scoville and B.G. White; Suitability and Efficacy of Crossover Drug Trial Designs in Epilepsy, by B. Scoville, B.G. White, J.J. Cereghino, and R.J. Porter; Clinical Trial Designs for the Efficacy Evaluation of Antiepileptic Therapies, by B.G. White and J.J. Cereghino; and ADD Program of NINCDS: Early Pharmacologic Evaluation of New Antiepileptic Drugs, by H.J. Kupferberg, E. Swinyard, and G. Gladding. In November 1980, an NINCDS grant-supported international symposium on status epilepticus, mechanisms and therapy, was held in Santa Monica, California. A monograph will be published from the contributions to this symposium; the editing of this volume is a major undertaking by the Epilepsy Branch.

An NINCDS research contract was awarded to the University of Washington to determine the effectiveness and safety of clorazepate dipotassium (Tranxene) as an adjunct to phenytoin in the treatment of complex partial seizures. This study showed that, as an adjunct, clorazepate is as effective as phenobarbital, provided fewer unwanted side effects, and was significantly preferred by patients. This study provided the pivotal data used by the Food and Drug Administration in 1981 to approve the indication of clorazepate as an adjunctive therapy for partial seizures.

The pharmacology laboratory of the Epilepsy Branch continues to provide support for the drug development program and to elicit information about the metabolism of antiepileptic drugs. The laboratory has worked closely with pharmaceutical industry sponsors of new compounds in the drug development program as they progress from screening to toxicity. New methodologies are developed to assay the drug in connection with its evaluation. For example, the metabolism of presently available drugs has been elucidated by I.M. Kapetanovic and H.J. Kupferberg in the following publications: Inhibition of Microsomal Phenobarbital Metabolism by Valproic Acid (Biochem Pharmacol 30:1361-1363, 1981) and Gas Chromatographic and Gas Chromatographic-Mass Spectrophotometric Determination of p-Hydroxyphenobarbital Extracted from Plasma, Urine, and Hepatic Microsomes (J Pharm Sci, in press).

Although most studies in epileptic animal models are in rodents, studies of spontaneous motor seizures in animals with chronic alumina foci have employed the primate to determine the pharmacokinetics and efficacy and safety of antiepileptic drugs since 1971. This model is close to the partial seizures seen in man and approximates the most severe adult problem in human epilepsy. A research contract with the University of Washington resulted in productive research over many years. This primate research contract was recompeted in 1980 and resulted in the award again to the University of Washington. Their research is expected to be enhanced by the addition of a biostatistician to the research team. This contractor is presently evaluating the efficacy of progabide and the pharmacokinetics of stiripentol, two potential antiepileptic drugs.

GRANT SUPPORTED RESEARCH

I. Introduction

Recent estimates indicate that epilepsy continues to be a severe public health problem in the United States. It is the second most commonly occuring neurological disorder, affecting one person out of every hundred or a total of more than two million people. In addition, four to five million people have experienced febrile seizures as children. Many epileptic subjects are well controlled, due largely to successful therapy with antiepileptic drugs, and are able to lead normal lives. However, it is estimated that 400,000 to 500,000 patients have recurrent, uncontrolled seizures. The physical and psychological consequences of uncontrolled seizures are devastating with marked decreases in life span and a high incidence of suicide in poorly controlled epileptic patients.

Epilepsy is a disorder resulting from abnormal excessive electrical discharges from one or more locations in the brain, which spread over normal or abnormal neuronal pathways. The development of an epileptic focus may arise following a wide variety of events, including fever, trauma, infection, anoxia, or tumors; in many patients, there is no apparent etiology. The location of the focus will determine the nature of seizures and the type of behavior associated with the seizure.

Research in epilepsy continues to advance on several broad fronts. Progress continues to be made in understanding the basic mechanisms which underlie epileptogenic events, as well as the means for controlling the generation and spread of seizure discharges in patients.

In FY81, the NDP received 137 applications for research and support of convulsive and related paroxysmal disorders of which 89 were approved and 20 funded for a total of $2,599,953. Of the funded applications, 15 were new or supplemental awards for $1,962,714. There are currently 81 active grants totaling $7,926,734.

Approximately four-fifths of the grants supported by the Epilepsy Branch are involved in the discovery of new information which sheds light on the basic processes responsible for generation, spread, and control of abnormal discharge in animal tissues. The remaining grants are dedicated specifically to the quest for understanding and control of seizures in humans. Three grants in particular are devoted to testing of new drugs or treatments to control seizures in epileptic patients.

II. Basic Mechanisms of Epileptogenesis

A total of 40 grants has as their primary objective an understanding of the basic mechanisms which cause seizures. One such study is defining the roles of cyclic AMP and GMP in cellular depolarization and seizure discharges. Results suggest that inhibition of cyclic AMP and cyclic GMP accumulation in depolarized brain tissue is a molecular/neuropharmacological action characteristic of antiepileptic drugs that have direct effects on cellular membrane function and electroshock seizures. Other results indicate that seizures augment release of catecholamines and adenosine from intracellular stores, and the action of these and other substances causes accumulation of cyclic AMP in epileptic brain. In contrast, cyclic GMP accumulates in epileptic brain as a result of a different presently undefined mechanism. These data further substantiate the hypothesis that cyclic nucleotides have important roles in epilepsy, and may explain some basic mechanisms of seizures and antiepileptic drug actions.

Five investigators are devoting their efforts to develop animal models of epilepsy which may be used as an aid in considering the causes and control of seizures. One model of particular interest is the immunoneurological model which provides a clearly defined target for studying molecular mechanisms. Recurrent seizure activity can be produced in rats and rabbits by injection of antiserum to the synaptic membranes of brain gangliosides. In other models, treatment of neonatal rats with an inhibitor of cholesterol synthesis results in the development of chronic epileptiform activity as evidenced by EEG changes later in life. Likewise, a strain of seizure-prone gerbils has been developed with the intention of determining the effects of nurturing and stressful conditions on the development of seizures. Other animal models previously established for the study of epilepsy continue to receive attention. Kainic acid, cobalt and penicillin are now commonly used agents for the production of epileptic phenomena in animals. The "kindling" effect is well established in monkeys and several investigators have applied the technique to smaller species.

Several investigators are concentrating on cerebral circulation and brain metabolism before, during, and after seizures. For example, it has been shown that when flux of methyl groups is altered, cells become seizure-prone. Others have shown that an alteration in serine flux is associated with oxidation of mitochondria and an increase in tissue levels of ammonia during seizures. In marmosets, significant decreases have been observed in myelin accumulation and protein synthesis as a result of seizures in the newborn period. Seizures can be induced in rat pups exposed to external heat, and the epileptiform activity is associated with large increases in metabolic activity, blood flow, oxygen and glucose consumption, and high-energy phosphate utilization.

Other investigators are examining the effects of seizures on ionic transport. One researcher has found that the rapid phase of spike frequency adaptation in invertebrates is sensitive to intracellular calcium. The entry of calcium activates a potassium conductance and may inactivate a sodium conductance. The slower phase also appears to be modulated by calcium transport.

III. Neurophysiological Studies

Local neuronal circuits are of interest to several investigators. The definition of circuitry is critical in discovering the mechanisms responsible for generation of epileptogenic events. One such study delineates the margins of an epileptic focus in terms of a retinal activation field, a circumscribed area in which stimulation by light evokes a characteristic epileptiform wave. Other studies involve the analysis of coupling between neocortical nerve cells in the somatosensory cortex of the rat. In ongoing studies of amygdaloid kindling, it has been shown that the positive transfer phenomemon is associated with abnormally facilitated accessibility of neuronal circuits to stimulation from the primary site of a focal epileptogenic process. Studies on nerve excitation indicate that some anticonvulsants may block frequency-dependent excitability primarily via their selective affinity for inactive sodium channels.

Investigations continue into the role of neurotransmitters in the production and spread of seizure discharges. One new investigator is examining the turnover of gamma hydroxybutyrate (GHB) and its precursors in pre- and postnatal rat brain.

GHB is a substance which appears to be a biologically active agent with an independent role and whose function in the development of epilepsy is unknown.

Six investigators are studying the pharmacology of anticonvulsant drugs and other agents and their roles in relation to the basic mechanisms of seizures. For example, it has been shown that phenytoin, carbamazepine, phenobarbital, primidone, phensuximide, and high concentrations of clonazepam inhibit veratridine-induced accumulation of both cyclic AMP and cyclic GMP. In contrast, ethosuximide, trimethadione, valproic acid, and low concentrations of clonazepam are ineffective or inhibit accumulation of cyclic GMP only. Another study is investigating changes in protein synthesis associated with increased cerebral excitability in the kindling phenomenon. It has been shown that phenytoin in therapeutic concentrations inhibits the calcium-dependent phosphorylation of particular brain proteins. The prolonged anticonvulsant actions of taurine and GABA are being examined by determining changes in free amino acid content in certain areas of the brain.

The effects of anticonvulsant drugs, as well as convulsant drugs, on GABA are being studied in nerve cell cultures. These investigations have suggested that postsynaptic modulation of GABA responses may underlie the basic mechanism of action of some antiepileptic drugs. One investigator, looking at the effect of GABA and phenytoin, suggests that phenytoin prolongs the open time of GABA-operated channels, rather than producing a partial blockage. Another study has shown that barbiturates may block synaptic ion channels. Other results have shown that the amplitude of the hyperpolarizing synaptic potential was greatly diminished by phenobarbital at concentrations which had no effect on pre- or postsynaptic potential.

An important factor in changes in neuronal excitability induced by kindling may be an alteration of synaptic sensitivity to neurotransmitters. Several investigators are attempting to elucidate the basic mechanism of epilepsy by examining changes in neuronal plasticity. Thus, it has been shown in numerous brain sites that kindling via one hippocampal afferent significantly facilitated kindling in the other--strong evidence that kindling trans-synaptically affects neuronal excitability. Additional data indicates an active role for catecholamines in this process of "positive transfer."

Twenty-four principal investigators are pursuing a line of basic research aimed at controlling the generation and spread of seizure discharges, either through an understanding of pharmacology or through development of new antiepileptic agents. A rat model has recently been developed for the study of posttraumatic epilepsy produced by the injection of iron salts. The experiments are designed among other things to study the effects of antiperoxidants on the development of seizures and histopathological lesions. The biochemistry of the central nervous system under various conditions designed to produce systemic ketosis is being investigated in an effort to understand the relationship between ketones, intracellular control mechanism of glucose, and the antiepileptic effect of ketosis. In particular, a study focusing on ketogenesis and cerebral glucose utilization has shown that an increase in energy reserves in the brain is caused by ACTH and glucocorticoids, resulting in increased cerebral ATP production. This suggests a possible mechanism for the clinical usefulness of ACTH in neurological disorders.

IV. Grant-Supported Drug Development

Seizures in many patients may be adequately controlled with medical therapy. However, despite decades of research, completely effective yet nontoxic antiepileptic drugs have not been found. To this end, the Epilepsy Branch is actively seeking to develop new drugs to treat epilepsy. In FY81, 16 grants were awarded to study antiepileptic drugs. Twelve grants were awarded to synthesize new and unique compounds for testing in the drug development program. Two grants aimed at the synthesis of congeners of established compounds. Compounds similar in structure to known anticonvulsants such as quinazolinones, oxopyrimidines, succinimides, and benzodiazepines have already been synthesized. Several new classes of compounds are being considered for further development and testing. Already, a series of derivatives of cannabinoids have been synthesized and are currently being evaluated for anticonvulsant effects in rats and rabbits. In addition, analogs and derivatives of apomorphine and aminoisoquinoline have been synthesized. Another study is aimed at synthesis of indole-related derivatives, similar in activity to the benzodiazepines. Further development of existing compounds continues. An N-alkylation procedure will produce several N-alkyl-substituted derivatives of hydantoins, barbiturates, cinnamic acid derivatives and pyrazolodiazepines. In addition, a series of novel sultams and lactams are being synthesized. A variety of compounds are being synthesized with structures based on the suspected involvement of GABA in some forms of epilepsy. This search for GABA-like agents or GABA-transaminase inhibitors offers significant promise in leading to useful agents. Another promising approach is the synthesis of drug and biological constituents such as cholesterol into complexes which would be incorporated semi-permanently into biological membranes. The stereochemistry of a number of existing anticonvulsants is being studied. Two additional grants were awarded to study structure-activity relationships. It has been shown, for example, that hydroxycarbamazepine has a spatial conformation similar to phenytoin. In addition, the spatial conformation of other new compounds, such as cannabidols, is being compared to existing anticonvulsants.

V. Epidemiology of Epilepsy

As noted above, 15 grants are supported in the area of research in human subjects. Three investigators are considering the epidemiology of epilepsy. The objective of one study is to investigate the genetic etiology of absence seizures by studying the genetic transmission of the disorder through intensive characterization of 8,000 kindred individuals. Another investigator is looking at the relationship between stressful life events and the occurrence of seizures, and determining if recall of recent stressful life events can activate epileptiform EEG abnormalities in epileptic patients. The third study is designed to investigate the higher incidence and mortality of epilepsy associated with a black population.

VI. Other Grant-Supported Epilepsy Research

Support is now being provided to three investigators for development of devices for automated detection, recording, and classification of epileptiform activity. These systems will ultimately allow mass screening of populations suspected of neurological disorders, as well as the optimal therapeutic management of epileptic subjects--a long-sought goal in epilepsy research. It is anticipated that this support of grant-related research will lead to an inexpensive, reliable, and portable multi-channel system to detect, record, and analyze both on- and offline cortex-derived epileptogenic spikes from multi-channel human scalp EEG data. To date, sufficient accuracy to permit widespread application of these techniques has not been achieved, but significant improvements are rapidly being made in the state-of-the-art methodology.

Slightly more than half the projects involving human research are devoted to the control of the generation and spread of abnormal discharges. Of these 8 projects, 5 are devoted to answering basic scientific questions in normal volunteers as well as patients, and the remaining 3 involve assessment of new methods of treatment for seizures in epileptic patients.

In terms of basic research in normal human volunteers, pharmacokinetic studies continue to elucidate the time course of absorption, distribution, metabolism and excretion of new as well as established antiepileptic drugs. Studies in normal volunteers receiving intravenous primidone showed one-half the dose was excreted intact with a half-life of 6 hours, one-sixth of the dose was converted to phenobarbital with a half-life of 76 hours, and one-third was converted to PEMA with a half-life of 16 hours. In chronically medicated patients, blood and urine levels were no different than in the normal volunteers. Other studies are considering the fate of phenobarbital and its major metabolites, including distribution into tissues. Species differences are also being investigated. More powerful analytical techniques have been developed for quantitation of carbamazepine, primidone, phenobarbital and several metabolites of the above compounds. Given that many currently available drugs are partially effective, the goal of these studies is to optimize therapy for the individual patient using scientific rather than empirical approaches.

In patients with temporal lobe epilepsy, intensive neuropsychological, physiological, and anatomical studies are being conducted prior to and after surgical ablation of the lesion in the temporal lobe.

Trials of nonpharmacological control of epilepsy in patients continues to be supported. In two studies, operant conditioning of the EEG has been shown in some patients to lead to a reduction in seizure rate.

Support continues for 8 program projects in epilepsy research, with numerous studies directed at the causes and treatment of seizures: one is devoted principally to the study of surgical therapy of temporal lobe epilepsy; 5 are a combination of clinical research and basic scientific studies; and 2 are strictly devoted to research in basic mechanisms of the generation and spread of seizure discharges.

With respect to the type of science base of the applications supported by the Epilepsy Branch, the grants are evenly distributed with 12 to 15 grants in each of 6 areas: biochemistry, neurophysiology, pharmacology, synthesis, clinical neurology, and other neurosciences.

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1980--September 30, 1981

UNIVERSITY OF VIRGINIA SCHOOL OF MEDICINE (N01-NS-9-2196)

Title: Absence Seizure Drug Studies and Long Term Followup of Patients with Absence Seizures

Contractor's Project Director: Fritz E. Dreifuss, M.D.

Current Annual Level: -0-

Objectives: To evaluate the effectiveness of combination valproic acid and ethosuximide on the frequency and intensity of absence (petit mal) seizures in patients who have failed to be controlled by ethosuximide or valproic acid alone. Prognostic evaluation of patients with absence seizures.

Course of Contract: The contract expired on 6/30/81 and the studies described above have been completed.

Major Findings: Following completion of the valproate controlled study, an open trial with simultaneous administration of valproic acid and ethosuximide was conducted. Fifteen patients with absence seizures who did not respond to either valproic acid or ethosuximide alone entered this study. Preliminary analysis shows that eight patients had 100% control; four, 75-99% control; one, 50-74% control; and two, no significant improvement. The detailed analysis of the result is yet to be made but our observation suggests that simultaneous administration is beneficial in some patients with intractable absence seizures. The prognostic study consists of 83 patients. There were 37 male and 46 female patients, 5.3 to 24.3 years of age (mean, 10.7 yr) at the initial examination. After follow-up periods of 4.6 to 14.3 yr (mean, 9.5 yr), the ages were 11.7 to 35.8 yr (mean, 20.1 yr) at the time of examination. At follow-up, 40 patients had no seizures of any type and 48 patients had ceased having absence seizures. All types of seizures had a good prognosis if the patient had a full-scale IQ of $\geqq 90$ ($p<0.02$) and a negative history of generalized tonic-clonic seizures ($p<0.01$). The prognosis of absence seizures was good with a full-scale IQ of $\geqq 90$ ($p<0.01$), a negative history of generalized tonic-clonic seizures ($p<0.01$), and a negative history of absence status ($p<0.01$). Mild, nonprogressive abnormalities were found in 9 of 78 patients who had CT scans.

Proposed Course: These studies have been completed. The results of follow-up study were presented at the Epilepsy International Congress in Kyoto, Japan, in September 1981.

Publications:

Sackellares JC, Sato S, Dreifuss FE, Penry JK: Reduction of steady state valproate levels by other antiepileptic drugs. Epilepsia (in press).

Sato S, Dreifuss FE, Penry JK, Kirby DD, White BG: Long-term follow-up study of absence seizures. Presented at Epilepsy International Congress, 1981, Kyoto, Japan, September 17-21, 1981.

C.T. No. 0700759

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1980--September 30, 1981

SOUTHERN RESEARCH INSTITUTE (N01-NS-0-2327)

Title: Studies of Toxicology and Selected Pharmacology of Potential Anticonvulsants

Contractor's Study Director: Robert G. Meeks, Ph.D.
Contractor's Study Supervisors: Kenneth Newman, D.V.M.
Keith Obrosky, Ph.D.

Current Annual Level: $477,057

Objectives:
1) Oral Toxicity of Candidate Anticonvulsant Compounds in Beagle Dogs and Rat: This portion of the toxicity evaluation exposes potential toxicologic effect of candidate anticonvulsant compounds on a variety of organ systems in the dog (beagle) and rat. Initial 14 to 28-day studies are to establish a dose-range for the longer 90-day oral toxicity studies. Changes in body weight and food consumption are presumptive indices for a toxicological effect. A gross necropsy is performed at the end of study and any remarkable changes in tissues are examined. Various hematological and biochemical parameters are also determined. The results of the dose-range finding studies are transmitted to the NINCDS Project Officer within 21 working days following termination. The 90-day oral toxicity studies in either rat or dog (beagle) are larger in scope than the dose-range finding studies. Hematologic biochemical and urinary parameters are monitored several times. Histopathologic examination of tissue is carried out on all animals in order to evaluate cellular changes. A final written report of all aspects of these studies are completed within 100 days of completion of the study.
2) Cardiovascular Response of Candidate Anticonvulsant Drugs in Unanesthetized Beagle Dogs: This phase of the project studies the effects of candidate anticonvulsant drugs on the cardiovascular system of unanesthetized beagles. The method used is designed to give maximum amounts of information without introducing artifacts into the data.
3) Cardiovascular Response of Candidate Anticonvulsant Drugs in Anesthetized Beagle Dogs: Beagle dogs are anesthetized, ventilated, and catheterized to measure the following parameters: (a) mean arterial blood pressure; (b) mean venous blood pressure; (c) mean pulmonary arterial pressure; (d) heart rate; (e) cardiac output; (f) maximum left ventricular change in pressure per unit of time; (g) systemic resistance; and (h) pulmonary vascular resistance.

Course of Contract: Over 30 compounds which have completed the early pharmacologic evaluation of the anticonvulsant drug screening contract have been reviewed by the Subcommittee on Anticonvulsant Drugs during the last two years. The Committee has established priorities for the toxicologic evaluation of the compounds. Supplies of several compounds (2-5 kg) were requested from the supplier, received by NINCDS, and sent to the contractor. A study number is assigned to each compound and a protocol is written by the contractor describing in detail each aspect of the study. The contractor must then follow the approved protocol. Any deviations or changes must be approved by the Project Officer. One 90-day oral toxicity in dogs, 3 to 4 90-day oral toxicity in rats, and 5 to 6 dose-range finding studies are expected to be carried out this year. The 3-year contract period ends February 27, 1983.

Proposed Course of Contract: The second year of the contract began on March 1, 1981. During the first year, two dose-range finding studies in beagle dogs were carried out followed by a 13-week (90-day) oral toxicity study with ADD 35 002. Two dose-range finding studies in rats were completed for ADD 09 004 and ADD 03 055. The second year saw the completion of the 13-week oral toxicity study of ADD 35 002 in beagle dogs and the initiation of a 13-week oral toxicity of ADD 03 055 in rats. Five dose-range finding studies and three 13-week oral toxicity studies in rats are planned for this year. Two new investigational drug applications (IND) will be prepared by the pharmaceutical industry sponsors from some of the data generated from the contract. The contractor has also developed the capability of determining homogeneity of compounds in suspension and new techniques for blood sampling from rats. These procedures will expedite the carrying out of the contract.

Publications: None

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1980--September 30, 1981

UNIVERSITY OF MINNESOTA (NO1-NS-0-2341)

Title: Epilepsy Information Transfer

Contractor's Project Director: Robert J. Gumnit, M.D.

Current Annual Level: $177,375

Objectives: The objective of this contract is to transfer information being generated from the Minnesota Comprehensive Epilepsy Program to all appropriate audiences. The materials and information being developed for all phases of epilepsy in this research program need to be rapidly transmitted to improve treatment for people with seizures. The contractor is providing support and coordination to established clinical and laboratory research programs by virtue of interdisciplinary interchange through methods such as inhouse conferences. The contractor is training and educating physicians and other professionals in the newest advances in epilepsy research and treatment in an effort to specifically increase and quicken the flow of information from clinical research. The contractor is establishing a broad program for public education to help disseminate the newest advances in epilepsy treatment.

Course of Contract: This project began September 30, 1980. The contractor is developing, testing, and implementing a broad program for professional education for the purpose of demonstrating to physicians and other professionals the newest in advances in epilepsy research and treatment. All types of epilepsy and all age groups are included. Efforts are being made to develop, implement, and scientifically evaluate programs to train those who serve patients with seizures. The contractor is also developing, testing, and implementing a broad program of public education for the purpose of improving public and patient knowledge about epilepsy. Efforts are being made to develop, test and implement public education programs and materials in cooperation with appropriate lay organizations; develop, test and implement educational programs for the patient; and use methods for interdisciplinary exchange to provide support and coordination to established clinical and laboratory research programs.

Proposed Course of Contract: This project will continue until September 29, 1983.

Publications:

Beniak J, Miller D, Blesi K: The reality of epilepsy: an up-to-date approach for patients and practitioners. *J Prac Nurs* 30:22-26, 1980.

Walton SAV: Teaching children about epilepsy. *Educ Unlim* 1:16-19, 1979.

Walton SAV: Epilepsy follow-up: dispensing facts, dispelling fears. *J Prac Nurs* 30:25-26, 39, 1980.

Walton SAV: What epilepsy is. *Early Years* 2(2):34 and 92, 1980.

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1980--September 30, 1981

Contractor		Project Director	Annual Level
Med Coll Georgia	(NO1-NS-6-2340)	J. Green, M.D	$1,198,712
Univ of Washington	(NO1-NS-6-2341)	A. Ward, Jr., M.D.	1,140,764
UCLA	(NO1-NS-0-2332)	A. Delgado-Escueta, M.D.	1,240,921

Title: Comprehensive Epilepsy Program

Objectives: The objective of the Comprehensive Epilepsy Program is to facilitate applied research and to coordinate research and teaching with health care services related to persons with all types of epileptic seizures within a defined geographic area.

Course of Contract: Each contractor is conducting clinical and laboratory research in the diagnosis, treatment, prognosis and prevention of epilepsy. Each contractor is demonstrating to physicians and other professionals the newest advances in epilepsy research and treatment and is establishing a broad program for public education. In addition, each contractor is establishing the required procedures to assure, in a research setting, the availability to the person with epilepsy of complete and up-to-date preventive medical and rehabilitative psychological, vocational, educational, and social services.

Major Findings: During fiscal year 1975 three Comprehensive Epilepsy Programs were established. During fiscal year 1976 two additional programs were established. An urban Comprehensive Epilepsy Program was established in 1980. All of the contractors showed evidence for the feasibility of establishing a program in their geographic area by a detailed description of clinical research capability, health care delivery capabilities, rehabilitation resources, etc., for the person with epilepsy. Two of these programs have undergone Technical Merit Review prior to beginning of the fourth year. Clinical research projects encompass etiology, epidemiology, diagnosis, and treatment.

Proposed Course of Contract: NO1-NS-6-2340 and NO1-NS-6-2341 are scheduled to expire contracts on 9/30/81. Grant funding has been obtained for NO1-NS-6-2341. NO1-NS-0-2332 will expire 6/30/83.

Publications:

MEDICAL COLLEGE OF GEORGIA

Akhtar RA, Aly MI, Abdel-Latif AA: Studies on the effects of sodium ion on the acetylcholine stimulated P32 labeling on phosphoionositide and the specific radioactivity of ATT32 of the rabbit iris smooth muscle and rat brain synapsomes. Biochem Biophys Res Comm, 1981 (in press).

Aly MI, Abdel-Latif AA: Studies on distribution and metabolism of valproate in rat brain, liver, and kidney. Neurochem Res 5:1231-1242, 1980.

Smith DB, Carl GF: Anticonvulsant folate interactions. In Dam M, Gram L, Penry JK (Eds): Advances in Epileptology: XIIth Epilepsy International Symposium. Raven Press, New York, 1981 (in press).

UNIVERSITY OF WASHINGTON

Batzel LW, Dodrill CB, Fraser RT: Further validation of the WPSI vocational scale: Comparisons with other correlates of employment in epilepsy. *Epilepsia* 21:235-242, 1980.

Bowdle TA, Levy RH, Cutler RE: Effects of carbamazepine on valproic acid kinetics in normal subjects. *Clin Pharmacol Ther* 26:629-634, 1979.

Bowdle TA, Patel IH, Levy RH, Wilensky AJ: Valproic acid dosage and plasma protein binding and clearance. *Clin Pharmacol Ther* 28:486-492, 1980.

Burgess ED, Friel PN, Blair AD, Raisys VA: Serum phenytoin concentrations in uremia. *Ann Int Med* 94:59-60, 1981.

Dikmen S, Reitan RM: MMPI correlates of adaptive ability deficits in patients with brain lesions. *J Nerv Ment Dis* 165:247-254, 1977.

Dodrill CB: Rapid evaluation of intelligence in adults with epilepsy. *Epilepsia* 21:359-367, 1980.

Dodrill CB: Interrelationships between neuropsychological data and social problems in epilepsy. In Canger R, Angeleri F, Penry JK (Eds): *Advances in Epileptology: XIth Epilepsy International Symposium*. Raven Press, New York, 1980, pp 191-197.

Dodrill CB: Neuropsychological evaluations in epilepsy. In Lockard J, Ward AA (Eds): *A Window to Brain Mechanisms*. Raven Press, New York, 1980, pp 231-241.

Dodrill CB: Objective assessment of psychosocial problems in epilepsy and its relevance to employment. In Kulig BM, Meinardi H, Stores G (Eds): *Epilepsy and Behavior '79*: Proceedings of WOPSASSEPY I. Swets and Zeitlinger B.V., Lisse, 1980, pp 140-148.

Dodrill CB, Batzel LW, Queisser HR, Temkin NR: Comprehensive care of the adult epileptic patient: an objective method for the evaluation of social and psychological problems. In Wada JA, Penry JK (Eds): *Advances in Epileptology: The Xth Epilepsy International Symposium*. Raven Press, New York, 1980, pp 395-400.

Dodrill CB: Neuropsychology of epilepsy. In Filskov SF, Boll TJ (Eds): *Handbook of Clinical Neuropsychology*. Wiley, New York, 1981, pp 366-395.

Dodrill CB: Neuropsychological assessment. In Troupin AS (Ed): *Management of Epilepsy*. Elsevier, Amsterdam, 1980 (in press).

Dodrill CB: Neuropsychology. In Laidlaw & Richens (Eds): *A Textbook of Epilepsy* (2nd Edition). Churchill, Livingstone, Edinburgh, 1980 (in press).

Dodrill CB and Batzel LW: Patterns of psychosocial problems in chronic epilepsy. In Dam M (Ed): *Proceedings of the Twelfth Epilepsy International Symposium*. Raven Press, New York, 1980 (in press).

Dodrill CB: An economical method for the evaluation of general intelligence in adults. *J Consult Clin Psychol*, 1981 (in press).

Fraser RT: Vocational aspects of epilepsy. In Hermann B, Hughes J (Eds): *A Multidisciplinary Handbook of Epilepsy*. Charles C Thomas, Springfield (Ill), 1980, pp 74-105.

Fraser RT, Austin MJ: The new challenges of personnel selection for rehabilitation and human services administrators. *J Rehab*, 1981 (in press).

Fraser RT: Developmental disabilities: A perspective for the mental health administrator. In Austin M, Hershey W (Eds): *Introduction to Mental Health Administration*. Jossey Bass, Monterey (Ca), 1981 (in press).

Friel PN, Leal KW, Wilensky AJ: Valproic acid - phenytoin interaction. *Ther Drug Monitor* 1:243-248, 1979.

Leal KW, Rapport RL, Wilensky AJ, Friel PN: Single dose pharmacokinetics and anticonvulsant efficacy of primidone in mice. *Ann Neurol* 5:470-474, 1979.

Levy RH: Monitoring of free valproic acid levels? (Commentary) *Ther Drug Monitor* 2:199-201, 1980.

Levy RH, Lai AA: A pharmacokinetic model for drug interactions by enzyme induction and its application to carbamazepine-clonazepam. In Johannessen SI, Morselli PL, Pippenger CE, Richens A, Schmidt D, Meinardi H (Eds): *Antiepileptic Therapy: Advances in Drug Monitoring*. Raven Press, New York, 1980, pp 315-323.

Levy RH, Lockard JS, Lane EA, Wilensky AJ: Preclinical evaluation of cinromide in the primate model: Relevance to the design of phase II clinical trials. In *Advances in Epileptology: XIIth Epilepsy International Sumposium*, Copenhagen, Denmark, September 6-10, 1980, Raven Press, New York, 1980 (in press).

Lovely MP: Identification and treatment of status epilepticus. *J Neurosurg Nurs* 12:93-96, 1980.

Miller ME, Ludwick BT, Ballard RH, Garland WA, Levy RH: Acetylation of clonazepam in fast and slow acetylators. *Clin Pharmacol Ther*, 1981 (in press).

Queisser HR, Armstrong HE, Jr, Smith WR, Davis GR: Psychoeducational skills training for individuals with epilepsy. In Upper D and Ross SM: *Behavioral Group Therapy: 1980 An Annual Review*. Research Press, Champaign, Ill, 1980, pp 219-234.

Raisys VA, Friel PN, Graaff PR, Opheim KE, Wilensky AJ: High-performance liquid chromatographic and gas-liquid chromatographic determination of diazepam and nordiazepam in plasma. *J Chromatogr* 183:441-448, 1980.

Wilensky AJ, Ojemann LM, Dodrill CB, Temkin NR: Difficulties in evaluating the efficacy of an anticonvulsant in the presence of other anticonvulsants. In Wada JA, Penry JK: *Advances in Epileptology: The Xth Epilepsy International Symposium*. Raven Press, New York, 1980, pp 329-334.

Wilensky AJ, Ojemann LM: Clinical evaluation of new antiepileptic drugs. In Lockard JS, Ward AA (Eds): *Epilepsy: A Window to Brain Mechanisms*. Raven Press, New York, 1980, pp 215-230.

Wilensky AJ: Antiepileptic drugs in the central nervous system. In Lockard JS, Ward AA (Eds): *Epilepsy: A Window to Brain Mechanisms*. Raven Press, New York, 1980, pp 201-213.

Wilensky AJ, Ojemann LM, Temkin NR, Troupin AS, Dodrill CB: Clorazepate (Tranxene (R)) compared to phenobarbital as antiepileptic drugs -- a double blind study. *Neurology*, 1980 (in press).

Wilensky AJ, Lane EA, Levy RH, Ojemann LM, Friel PN: Differential kinetics in cinromide and two of its metabolites in epileptic patients. *Eur J Clin Pharmacol*, 1981 (in press).

Wyler AR, Robbins CA, Dodrill CB: EEG operant conditioning for control of epilepsy. *Epilepsia* 20:279-286, 1979.

Zimmerman CL, Patel IH, Levy RH, Edwards D, Nelson SD, Hutchinson M: Protein binding of valproic acid in the presence of elevated free fatty acids in patient and human plasma. *Epilepsia* 22:11-17, 1981.

UCLA

Cornford E, Crane PD, Braun LD, Bocash W, Nyerges AM, Olderdorf WH: Reduction in brain glucose utilization rate after tryptophol (3-Indole ethanol) treatment. *J Neurochem*, 1981 (in press).

Escueta AV-Delgado, Bacsal F-Enrile, Treiman DM: Complex partial seizures on the CCTV-EEG: a study of 691 seizures in 79 patients. *Ann Neurol*, 1981 (in press).

Escueta AV-Delgado, Treiman DM, Bacsal F-Enrile: Phenotypic variations of seizures in children and adults. In Anderson E, Hauser A (Eds): *Genetics and Epilepsy*. Raven Press, New York, 1981 (in press).

Treiman DM, Escueta AV-Delgado: Episodic loss of consciousness. *Drug Ther* 10:112-124, 1980.

Treiman DM: Seizure types and causes of epilepsy. In Walter RD (Ed): *Epilepsy: Seminars in Neurology*, 1981.

Walter DO: Computer analysis of the synthesizing brain. In *Proceedings of the 1981 International Conference on EEG and EMG Data Processing*. Elsevier/North-Holland Biomedical Press, 1981 (in press).

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1980--September 30, 1981

THE METHODIST HOSPITAL (Houston, Texas) (N01-NS-9-2321)

Title: Treatment of Infantile Spasms

Contractor's Project Director: Peter Kellaway, Ph.D.

Current Annual Level: $130,000

Objectives: To conduct a double-blind controlled crossover evaluation of corticotropin and prednisone in 25 patients with infantile spasms. Children who do not respond to either treatment will be administered clonazepam in an open trial. Precise quantitation methods were developed in a predecessor contract.

Course of Contract: This contract began September 28, 1979. In the first 20 months, 17 patients have entered into the study; 13 of these have completed the protocol. Of these, 4 responded to the initial drug, 5 to the crossover drug, and 4 did not respond to either treatment. Four patients entered the open clonazepam trial, none of whom responded. Five patients developed hypertension, a side effect of corticotropin. One patient developed cutaneous herpes. It is projected that all 25 patients will complete the study early in 1982.

Major Findings: A comparison of the three drugs used (corticotropin, prednisone, and in failures, clonazepam) may be made when the study is completed in 1982.

Proposed Course of Contract: This contract will end with the completion of 25 patients in 1982. The methodology employed to evaluate the treatment of infantile spasms (video recording, electroencephalograms, and accelerometry) will be adapted for use in another study. Roche Laboratories will support a clinical evaluation of nitrazepam in infantile spasms. Dr. Kellaway will serve as a consultant to the study; the Epilepsy Branch is cooperating in protocol development and data interpretation and analysis.

Publication:

Hrachovy RA, Frost JD Jr, Kellaway P, Zion T: A controlled study of ACTH therapy in infantile spasms. Epilepsia 21:631-636, 1980.

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1980--September 30, 1981

UNIVERSITY OF WASHINGTON (N01-NS-1-2349)

Title: Study of Experimental Anticonvulsant Drugs in Primates

Contractor's Project Director: Joan S. Lockard, Ph.D.

Current Annual Level: $459,000

Objectives: To compare the anticonvulsant efficacy of drugs in primates with spontaneous motor seizures. Seizure frequency and behavioral toxicity are compared with drug dosage and drug blood concentration. Metabolic and pharmacokinetic studies are conducted prior to efficacy determination.

Course of Contract: A predecessor anticonvulsant drug research contract in the primate was awarded competitively in June 1971, and was considered highly effective and productive. The first 18 months were devoted to the validation of the primate model of focal seizures. A series of quantitative drug evaluations were then performed. These studies were efficacy of anticonvulsants, documentation of the role of social factors in drug therapy, single dose pharmacokinetic experiments, long-term studies, and mass spectrometry of metabolites of anticonvulsant drugs. A Request for Proposals issued in FY80 resulted in the award of the present 3-year contract, again to the University of Washington, effective February 16, 1981.

Major Findings: Under the present contract, the Co-Principal Investigator is determining the pharmacokinetics of stiripentol, while the Principal Investigator studies the efficacy of progabide. The predecessor contract provided data on the solubility and stability of progabide. Kinetic studies revealed this drug has a large clearance, large volume of distribution, and a short biologic half-life (less than 1 hour) in the monkey. Two metabolites--an acid and benzophenone--have been identified. In an efficacy evaluation, the major metabolite of cinromide, 3-bromocinnanamide, was found to reduce seizure frequency and/or duration in half of the 6 monkeys studied. The primate model was itself investigated, showing that the epilepsy incident to alumina injection into the sensorimotor cortex in the monkey is not dependent on the continual presence of alumina and is not associated with independent (mirror) foci.

Proposed Course of Contract: A significant change in the research undertaken is the inclusion of a biostatistician in the development of research plans and later analysis. It is anticipated that this change will enhance the research and add to the validity of findings. The contract will be site visited in FY82. This contract expires January 15, 1984.

Publications:

Bowdle AT, Patel IH, Levy RH, Wilensky AJ: Valproic acid dosage and plasma protein binding and clearance. Clin Pharmacol Ther 28:486-492, 1980.

Harris AB, Lockard JS: Absence of seizures or mirror foci in experimental epilepsy after excision of alumina and astrogliotic scar. Epilepsia 22:107-122, 1981.

Koch KM, Ludwick BT, Levy RH: Phenytoin-valproic acid interaction in rhesus monkey. Epilepsia 22:19-25, 1981.

Lai AA, Levy RH, Martis L: Pharmacokinetic profile of valproic acid in rhesus monkeys following single bolus and constant rate intravenous administrations. Therapie 35:221-232, 1980.

Levy RH: Phenytoin: biopharmacology. Adv Neurol 27:315-321, 1980.

Lockard JS, Congdon WC, DuCharme LL, Finch CA: Slow-speed EEG for chronic monitoring of clinical seizures in monkey model. Epilepsia 21:325-334, 1980.

Lockard JS, Levy RH, DuCharme LL, Congdon WC: Cinromide's metabolite in monkey model: gastric administration and seizure control. Epilepsia 21:177-182, 1980.

Patel IH, Levy RH, Cutler RE: Phenobarbital-valproic acid interaction. Clin Pharmacol Ther 27:515-521, 1980.

Patel IH, Levy RH, Neal JM, Trager WF: Simultaneous analysis of phenobarbital and p-hydroxyphenobarbital in biological fluids by GLC-chemical-ionization mass spectrometry. J Pharm Sci 69:1218-1219, 1980.

Rapport RL II, Harris AB, Lockard JS, Clark AF: $Na^+ + K^+$-ATPase in serially excised segments of epileptic monkey cortex. Epilepsia 22:123-127, 1981.

Warren JW Jr, Benmaman JD, Wannamaker BB, Levy RH: Kinetics of a carbamazepine-ethosuximide interaction. Clin Pharmacol Ther 28:646-651, 1980.

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1980--September 30, 1981

UNIVERSITY OF KANSAS MEDICAL CENTER (N01-NS-2-2313)

Title: Investigation of Pharmacologic Posttraumatic Epilepsy Prophylaxis

Contractor's Project Director: Charles Brackett, M.D.

Current Annual Level: $100,000

Objectives: The main objective of the study was to determine the effectiveness of therapeutic treatment with phenytoin and phenobarbital in persons who suffer severe head injury and are thus liable to posttraumatic epilepsy. This study was preceded by a pilot study with prophylactic doses in less severely head injured patients. The patients admitted to the severely injured protocol will be followed an additional 18 months to provide information about the occurrence of "late" seizures.

Course of Contract: In the completed pilot study, 125 patients were accessioned to the protocol in which either phenobarbital 60 mg and phenytoin 200 mg or placebo were given to head injured patients daily for 18 months. These patients were then followed an additional 18 months. Eleven patients experienced seizures while on study and four had seizures after completion of drug therapy. No significant difference in seizure incidence was found between the active and placebo groups on the low drug doses used. Results of this pilot study are currently in preparation for publication.

The pilot study results led to the second phase of the contract work. Forty-nine patients were accessioned to the revised protocol in which patients randomized to active drug received higher, individualized therapeutic doses of phenytoin and phenobarbital for six months. Therapeutic range was achieved and maintained by frequent blood level analysis and dose adjustment. These patients were then followed an additional 12 months for seizure frequency. Ten patients experienced seizures while on the study (2 active and 8 placebo). The preliminary analysis of the 49 patients in this series indicates that those patients with phenytoin and phenobarbital in therapeutic doses had a significantly lower incidence of posttraumatic epilepsy than those untreated.

Proposed Course of Contract: The overall results of the pilot study are being prepared for publication. Because of the very protracted period of time during which posttraumatic epilepsy may develop, and the highly variable incidence of seizures occurring with the different types of severe head injuries, the patients in the Phase II study will continue to be followed for at least an additional 18 months. This will provide for the collection of sufficient data to allow for inferences to be made regarding the occurrence of "late" seizures.

Publications: None.

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1980--September 30, 1981

EXCERPTA MEDICA FOUNDATION (N01-NS-3-2303)

Title: Publication of *Epilepsy Abstracts*, Volume 14

Contractor's Project Director: Pierre Vinken, M.D.

Current Annual Level: $55,000

Objectives: To scan serial publications and periodicals from approximately 3500 world biomedical journals and select appropriate articles to be included in *Epilepsy Abstracts* in accordance with the guidance of the Project Officer and his editorial advisors; prepare abstracts with appropriate translations into English from foreign languages; classify, index, and store the abstracts in a computer retrievable form; and produce a 9-tract, 1600 bpi computer tape for use at NIH. The text is automatically set by computer-operated photocomposition. The Excerpta Medica Foundation produces camera-ready copy for each monthly issue of *Epilepsy Abstracts*, which includes an index of subjects and authors, and prints and distributes the journal monthly with a cumulative index at the end of the volume. In order to pay for the production of the camera-ready copy, printing, and distribution, the Excerpta Medica Foundation sells subscriptions to recover these costs.

Course of Contract: Subscriptions to *Epilepsy Abstracts*, each at annual cost of $77.00, have been acquired from interested persons by Excerpta Medica at a satisfactory rate. Interest in the publication continues at a high level throughout the world.

Proposed Course of Contract: Continued publication of monthly issues of *Epilepsy Abstracts*; computer tapes delivered to NIH bimonthly in accordance with the contract. These tapes comprise the EPILEPSYLINE data base retrievable throughout the country from B.R.S., Inc.

Publications: None.

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1980--September 30, 1981

UNIVERSITY OF UTAH (N01-NS-0-2335)

Title: Early Pharmacologic Evaluation of Anticonvulsant Drugs

Contractor's Project Director: Ewart A. Swinyard, Ph.D.

Current Annual Level: $494,835

Objective: To determine the anticonvulsant properties of novel organic compounds at various levels of testing from preliminary screening to extensive activity and toxicity profiles.

Course of Contract: Compounds are received by NINCDS from academic and industrial medicinal chemists and then are sent to the University of Utah for evaluation. The initial phase of the contract is to test all compounds for anticonvulsant and neurotoxic activity over a wide dose range. The median effective dose (ED_{50}) and the median toxic dose (TD_{50}) are determined for those compounds which possess significant activity in the initial evaluation. These parameters are determined at time of maximal pharmacologic activity following intraperitoneal administration. The compounds are evaluated for their ability to raise seizure threshold and/or prevent seizure spread. The data is analyzed and reviewed by the NINCDS staff and the results are transmitted to the suppliers of the compounds. Additional supplies of the most promising candidate compounds are obtained for advanced testing. A complete profile of acute neurotoxicity in mice following intraperitoneal administration of the candidate compound is determined, of which the median hypnotic dose (HD_{50}) and median lethal dose (LD_{50}) are included in the third phase of evaluation. The fourth phase includes the estimation of the median effective anticonvulsant dose and the median neurotoxic dose following oral administration. The fifth phase evaluates the median effective dose (ED_{50}) of candidate compounds for the ability to inhibit threshold seizures induced by bicuculline and picrotoxin and tonic seizures induced by strychnine. Phases 6 and 7 are carried out in rats. In Phase 6, the median effective anticonvulsant dose (ED_{50}) and the median neurotoxic dose (TD_{50}) are determined following oral administration. In Phase 7, the minimal lethal dose following chronic administration (5-day) is established along with its effect on anticonvulsant activity.

Proposed Course of Contract: This contract began October 1, 1980 for a 3-year period. During the first half of the contract year, approximately 542 compounds were screened in Phase 1. Currently, 100 compounds are scheduled for advanced phase testing. Six compounds have completed all phases and were reviewed by the Subcommittee on Anticonvulsant Drugs for further testing within the Antiepileptic Drug Development Program.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02511-01 EB

PERIOD COVERED October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Development of Analytical Methods of Analysis for Potential Anticonvulsants

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	Harvey J. Kupferberg	Pharmacologist	EB NDP NINCDS
Others:	Wayne Yonekawa	Pharmacologist	EB NDP NINCDS
	Jill Shaw	Medical Technician	EB NDP NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Epilepsy Branch, NDP, NINCDS

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.5	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Analytical methods for the quantitation of drugs are needed for the various phases of drug development. These methods must have specificity and sensitivity to quantitate drugs in dosage forms of the toxicology study, and in body fluids for human pharmacokinetic and efficacy studies. Chromatographic methods are most useful for this purpose. Drugs are extracted. The physical and chemical characteristics of each compound is evaluated in order to determine the suitable chromatography and detection. Volatile compounds are subjected to gas-liquid chromatography (GLC). Polar compounds are quantitated by high pressure liquid chromatography (HPLC). Extraction procedures for a variety of compounds were developed using a preferential solvents systems theory. The final methods were found to be suitable for a variety of both animals and humans.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To develop methods of analysis for a variety of different chemicals having potential antiepileptic activity in humans.

Major Findings: High pressure liquid chromatography and gas-liquid chromatograph in combination with specific detectors (e.g., fluorometric, electron-capture, electrochemical) can be used in quantitating a number of potential antiepileptic agents in biologic fluids and in a variety of dosage forms.

Significance to NINCDS Program and Biomedical Research: The determination of amounts of drugs in different biologic fluids are needed for a drug development program. Assurance of dose potency in a toxicology program is a part of the preclinical Good Laboratory Practices (GLP) requirement. Plasma level determinations of antiepileptic drugs are needed for clinical pharmacokinetic and efficacy studies in humans. These methods must be specific and sensitive for each individual segment of a drug development program.

Proposed Course: Methods of analysis for several ADD drugs have been developed.
1) ADD 35002: HPLC - fluorometric detector
2) ADD 03055: HPLC - ultraviolet detector
3) ADD 03046: GLC - electrocapture detector
4) ADD 76002: HPLC - electrochemical detector
Methods of analysis for ADD 40016 and 41004 are now being developed. New compounds selected for advanced testing will be considered for method development.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02512-01 EB

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Inhibition of Microsomal Primidone Metabolism by Phenytoin

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	Maria G. Porro	Pharmacologist	EB NDP NINCDS
Others:	Harvey J. Kupferberg	Pharmacologist	EB NDP NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Epilepsy Branch, NDP, NINCDS

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0.5	PROFESSIONAL: 0.5	OTHER: 0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Phenytoin has been reported to cause an elevation of plasma phenobarbital in epileptic patients. Phenytoin has been shown in patients to 1) stimulate the metabolism of primidone to phenobarbital and 2) inhibit the hydroxylation of phenobarbital. The concomitant rise in phenobarbital levels can cause sedation in epileptic patients. The use of an in vitro system of hepatic microsomes can be of benefit in elucidating the mechanism of this drug-drug interaction. Microsomes will be obtained from adult male phenobarbital-treated Holtzman rats. The rate of phenobarbital production from primidone and the hydroxylation of phenobarbital will be followed at 37°C in a NADPH and NADP system. The Michaelis constant (K_m) Maximal Velocity (V_{max}) will be determined for the conversion of primidone to phenobarbital and for the conversion of phenobarbital to hydroxyphenobarbital. The inhibition constant (K_I) will be determined for phenytoin in this system.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To determine the biochemical mechanism of phenytoin's inhibition of primidone/phenobarbital metabolism.

Major Findings: Project in progress.

Significance to NINCDS Program and Biomedical Research: This investigation will provide an understanding into the mechanism of drug-drug interaction observed in epileptic patients.

Proposed Course: The data gathered from these *in vitro* studies will be compared to the values found in epileptic patients. Other *in vitro* systems will also be investigated.

Publications: None

TAB 5.B -- DEVELOPMENTAL NEUROLOGY BRANCH -- DNB/NDP

ANNUAL REPORT

October 1, 1980 through September 30, 1981

Developmental Neurology Branch, NDP
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

RESEARCH SUMMARY

I. Introduction 1

II. Disorders of Early Life 2

III. NINCDS Collaborative Perinatal Project 8

IV. Additional Activities 18

CONTRACT NARRATIVES

Combined Neuropathologic and Epidemiologic Study
N01 NS 3-2312 20

Physical Growth Analysis
N01 NS 5-2308 21

Analysis of General and Placental Pathology Data
N01 NS 7-2376 23

A Prospective Cohort Epidemiologic Study of Learning Handicaps in Children Attending School
N01 NS 7-2377 25

Comprehensive Study of Labor and Delivery Effects on Offspring
N01 NS 8-2381 26

RESEARCH PROJECTS

The Genetics of Intellectual and Motor Performance
Z01 NS 01857-12 DNB 27

Convulsive Disorders Data Analysis Group
Z01 NS 02058-09 DNB 28

Cerebral Palsy Data Analysis Group
Z01 NS 02059-09 DNB 31

Birthweight-Gestational Age
Z01 NS 02060-09 DNB 34

Table of Contents (cont'd)

Minimal Brain Dysfunction
Z01 NS 02062-09 DNB 35

Developmental Factors Associated with Mental Retardation
Z01 NS 02106-08 DNB 37

The Study of Visual Abnormalities in the NINCDS Collaborative Perinatal Project
Z01 NS 02107-08 DNB 39

Developmental Factors Associated with Learning Disorders
Z01 NS 02108-08 DNB 40

Comprehensive Analysis of the NCPP Data on Congenital Malformations
Z01 NS 02109-08 DNB 42

Neonatal Hyperbilirubinemia
Z01 NS 02112-08 DNB 49

Obstetrical Medication and Development in Infancy and Early Childhood
Z01 NS 02169-07 DNB 50

Compendium of Heritable Disorders of the Nervous System
Z01 NS 02171-07 DNB 51

Febrile Seizures Study
Z01 NS 02234-06 DNB 53

Analysis of NCPP Twin Data
Z01 NS 02332-04 DNB 56

Genetic Bases of Neonatal Reflexes
Z01 NS 01274-17 DNB 58

ANNUAL REPORT
For Period October 1, 1980 through September 30, 1981
Developmental Neurology Branch, Neurological Disorders Program
National Institute of Neurological and Communicative
Disorders and Stroke
National Institutes of Health

GENERAL SUMMARY

INTRODUCTION

The Developmental Neurology Branch (DNB) develops and implements a program of research on the neurobiological aspects of the developmental disorders of children including cerebral palsy and other motor disorders, autism and behavioral disorders, mental retardation and learning disorders, and central nervous system birth defects and genetic disorders. The DNB is formally organized into sections which correspond to these four subprogram areas. During this year the DNB administered all grants classified as Disorders of Early Life, a major disorder category within the Neurological Disorders Program.

New initiatives are being developed by the DNB in Reye's Syndrome, neonatal brain disorders, neural tube defects, neurophysiology of learning disorders, and a study designed to measure the effects of phenobarbital therapy on the cognitive and neurological status of the treated child who has experienced febrile seizures.

A program announcement on Reye's Syndrome was sponsored by NINCDS and published on May 16, 1980 which requested individual and program project research grant applications. This program announcement was co-sponsored by three other NIH institutes. The DNB served as the focal point within the NINCDS in the planning of a Consensus Development Conference on the Diagnosis and Treatment of Reye's Syndrome which was held on March 2-4, 1981. The NINCDS was the lead agency for this Consensus Conference in co-sponsorship with the Office for Medical Applications of Research, NIH, the Center for Disease Control, the National Center for Health Statistics and the following NIH institutes: NIAID, NICHD, NIAMD, NIGMS, and NIEHS. The Consensus Conference focused on the criteria for diagnosis and on the treatments in use, with particular attention to the treatment of the syndrome as a function of the severity of the syndrome. The Consensus Statement will be widely disseminated and papers presented at the conference will be published.

The initiative on neonatal brain disorders focuses on the pathogenesis, diagnosis, treatment, and outcome of intraventricular hemorrhage in low birthweight neonates, hypoxic-ischemic encephalopathy in full-term infants, neonatal seizures, and metabolic disorders relevant to neonatal brain function. A program announcement was published on January 2, 1981 which requested program project grant applications focused on clinical research.

The effect of anticonvulsant medication, particularly phenobarbital, on the developing nervous system has been a major concern of the DNB. The Consensus

Conference on Febrile Seizures held in May of 1980 also emphasized this concern, and a program initiative is underway which will study delays in the development of cognitive and neurological function as a result of long-term phenobarbital therapy in children who have experienced febrile seizures. A Request for Contract Proposal (RFP) was issued on March 13, 1981 entitled "Behavioral and Cognitive Side Effects of Phenobarbital Used for Prevention of Febrile Seizure Recurrence".

The DNB has continued a major effort during this fiscal year to meet the objectives of the Comprehensive Plan for Analysis and Interpretation of NINCDS Collaborative Perinatal Project (NCPP) Data. A major area of the Comprehensive Plan was completed during the year: a book dealing with minimal brain dysfunction in NCPP children was published. Also, during the year a total of 64 papers were published or are in press; these papers are cited in the body of the report. As the NINCDS will soon complete its use of the Collaborative Perinatal Project data, an RFP will be issued which proposes to contract for the production of a Users Guide to the NCPP data with long-term management of the microfilm and computer tape files as a national data resource for bona fide biomedical/behavioral researchers by the National Archives.

Other activities of the DNB include primary responsibility for administering the Privacy Act within the NINCDS, conducting reviews of NINCDS research contract proposals to assure the protection of human subjects, and committee participation in planning and implementing the equal employment opportunity contract compliance program of the NIH.

II. DISORDERS OF EARLY LIFE

Reye's Syndrome

Reye's Syndrome is a disease of children which was first recognized and described by R. D. K. Reye in 1963. The disease is characterized by the sudden onset of intractable vomiting, and changes in mental status. If untreated, the disease may rapidly progress to coma. Mortality is high when coma develops and 15-25 percent of hospitalized cases have a fatal outcome. Since the disease is not among those whose occurrence must be reported, statistics on its national prevalence are difficult to obtain. Typically, the disease occurs a few days following a viral infection. The viruses most commonly associated have been influenza B and varicella (chickenpox). In addition to the neurologic signs of lethargy, limited attention span, and then coma, the disease also presents with dramatic biochemical abnormalities. Patients usually have hyperammonemia as well as an increase of serum fatty acids. Impaired liver function may be highly suggestive when observed in conjunction with clinical symptoms. Microscopic examination of liver from patients with active disease reveals excessive fatty infiltration of the liver and structural alterations of the mitochondria in liver cells. The changes in blood chemistry and liver function are thought to be responsible for the most prominent feature of the disease, the acute brain pathology which typifies the syndrome. Severely ill patients may rapidly progress to deep coma and death. Currently the institute is supporting research on the neuropsychological consequences of Reye's

Syndrome, and on metabolic profiles and amino acid disorders in the syndrome. Research on a "serum factor" identified uric acid as the factor, but subsequent work has suggested that the serum may contain another factor which plays a role in the etiology. The response to the program announcement has been good, and a number of new research grants on Reye's Syndrome are anticipated.

Cerebral Palsy and Motor Disorders

A major initiative in the area of neonatal brain disorders through program project research grants has begun. Because of the increasing success in the prevention of hyaline membrane disease, neonatal brain disorders have become more important as major contributors to mortality and morbidity, including, most probably, many of the motor disorders of childhood. Response to the program announcement has resulted in a number of applications which will receive peer review during the remainder of FY '81 and '82. There is a rapidly expanding knowledge base and new technologies are available to study these disorders; thus the timing appears right to launch such an effort. Grants currently funded and related to this general area include the following: A project is underway to better understand the pathogenesis of common clinical diseases relating to the central nervous system in infants and children and a biochemical (metabolic) rationale for therapy. Studies of an animal model in which variable hypoxic insults are administered to newborn rats, with emphasis on maturation of the central nervous system have shown that the rat is surprisingly resistant to hypoxic insult, although some differences were noted in growth and development. Studies of another animal model in which the response of the neonatal cerebral circulation to acute asphyxia is examined in relation to the role of the sympathetic nervous system have shown that hyperemia is more prominent in hindbrain than in forebrain. A study of placental pathologies as they mediate or serve as predictors of neurologic abnormalities in children is underway; this study was formerly funded under the contract mechanism and results are reported in a Contract Narrative elsewhere in this report (The Pennsylvania State University, Contract NO1-NS-7-2376).

In the general area of motor disorders and spasticity current grants include the following: A study to evaluate the methodology in measuring resistance to passive joint movement in patients with cerebral palsy is underway. Another study is developing objective tests of motor performance in patients with CP and will evaluate the effects of cerebellar stimulation in these patients; testing of spinal reflexes has indicated that these reflexes are very different in CP and adult CNS injury, implicating a developmental error in CP. A project to assess pharmacological treatments for patients with movement disorders is in progress and improvements in movement have been noted under some drug regimens. An animal research study is addressing early anatomical development of motor cortex, including behavioral development of fine hand movements. A new grant was funded for this fiscal year to study, for the first time in a controlled and systematic fashion, the efficacy of physical therapy in the treatment of cerebral palsy (CP).

Studies of plasticity offer hope for a basic neurobiological understanding of the processes of nerve growth and regeneration following the onset of pathological processes or other insults to the central nervous system. Hopefully, these and similar basic studies will eventually point the way toward more effective therapy. Active grants include a neuroanatomical study of the morphological plasticity of the hippocampus in sub-human primates following brain lesions; the major discovery this fiscal year was the finding that each of the principal fields of the hippocampus proper comprises a homogeneous population of neurons whose efferents are distributed to different sites. Other studies include investigations of alterations in neuronal pathways and connections which develop after specific brain lesions are inflicted in neonatal rats, and a study of the changes in anatomical pathways and functional recovery in the corticospinal system of rats who have received surgical lesions or irradiation early in life. A new grant designed to assess the structural and functional plasticity of the prefrontal region of the brain of sub-human primates following fetal or neonatal injury is underway. This work will attempt to elucidate basic principles and mechanisms and may lead to discovery of preventive and therapeutic measures in human cases of brain injury; findings to date include: (a) that sparing of delayed response function after unilateral brain injury is age dependent; (b) that sparing of delayed response following perinatal brain injury exacts its cost in terms of lowered capacity; (c) that cortical striatal projections show maturity one month before birth; (d) that dopamine agonists may be suitable treatment for dementia; and (e) that thiamine deficiency produces a cognitive defect.

Developmental Neurobiology and Behavioral Studies

Nerve Growth Factor. Nerve growth factor (NGF) is necessary for the growth and development of sensory and sympathetic neurons. Several basic and comprehensive biochemical studies are being carried out to define: 1) the molecular structure of NGF; 2) its biological roles in the development and maintenance of the peripheral nervous system; 3) the interaction of NGF with its receptors which leads to changes in gene expression in the responsive cells. One study has reported that with a low concentration of calcium, NGF-elicited neurite outgrowth in embryonic sensory neurons fails to occur. Another group of investigators has found striking *in vivo* control of sympathetic neuron morphology by locally applied NGF, suggesting that spatial and temporal variations in NGF levels in the developing organism may control where sympathetic axons grow and survive, and where they branch extensively and produce sites of transmitter release. One study has as its goal the important objective of identifying and characterizing mammalian NGF from sources other than the mouse salivary gland. It is expected that knowledge of the structure and function of NGF can be applied in studies of several disorders including neuropathies involving neurons that require growth factors, idiopathic orthostatic hypertension, and familial dysautonomia. These studies are also expected to help understand the basic mechanisms in neurofibromatosis.

Nutrition and Toxicity. In the area of nutrition, a study of the effects of vitamin B-6 deficiency on the developing CNS has as its goals: 1) to determine relationships between marginal levels of B-6 fed to the mother during growth, gestation, and lactation and measurements of CNS development in the progeny; and (2) to correlate CNS morphology in the progeny with the behavioral symptoms associated with low dietary levels of vitamin B-6. It has been found that the most restrictive maternal diet leads to gross neurological signs of B-6 deficiency in the progeny related to reduced brain myelination.

The effects of several toxic agents on developing CNS are being investigated. In a study of the effects of drugs on neurochemical maturation of the brain, neonatal and adult rats were treated chronically with haloperidol. It was found that dopamine neurons develop tolerance after chronic haloperidol treatment. The increase in turnover of dopamine reported to follow a single injection of haloperidol did not occur. Tolerance was similar in neonatal and adult rats suggesting that the dopamine containing neurons mature functionally very soon after birth. A study of neurochemical and neurophysiological effects of exposure to halothane in rats has shown that while postnatal exposure affects brain myelination, prenatal exposures have little or no effect on subsequent brain myelination or synthesis of non-myelin subcellular fractions. Another study is underway to examine the effects of organic tin, lead and mercury on myelinogenesis, myelin maturation, and axonal transport in the peripheral and central nervous systems. The objective is to test the hypothesis that an early effect of chronic heavy metal intoxication is an alteration in the synthesis or maintenance of one or more nervous system membranes. The effects of a relatively low level of X-irradiation on the morphology of the developing CNS and the behavioral expression of these changes (neurological status, hyperactivity) are being investigated in rats and chickens.

Behavioral Development. Studies of electrophysiological indices of functional hemispheric asymmetry have shown differences in EEG and in reaction time as a function of tasks that differentially activate neural mechanisms within the two hemispheres. Relationships between EEG asymmetry and learning are also being investigated. Findings from a study of brain mechanisms of behavioral dimorphism indicate that hormonal differences between the sexes or more direct hormonal manipulations may have effects on neuronal morphology. Loss as well as growth of neuronal process, particularly in the preoptic area, may be involved in the generation of sexually dimorphic patterns of brain growth. In another study, the long term objective is to establish a model system in which to identify morphological changes responsible for behavioral changes in development. The model system used is the transition from thermotaxis to olfactory orientation that occurs during the second week of life in the golden hamster. In a study of functional effects on neurobehavioral development, quantified behavioral and neuroanatomical data are being collected to test the hypothesis that neural development is responsive to and normally dependent on functional activity (motility) during embryonic and larval stages of development. The important roles of experience in the later perinatal and postnatal periods have already been demonstrated. Another study focuses on the relationship between behavioral arousal in the first postnatal month of the rat pup and the maturation of dopamine (DA) and noradrenergic (NE) systems in the rat brain. In experiments manipulating central DA and NE mechanisms, results indicate a peak effect of apomorphine on general activity at three weeks of age in normal pups. Results also suggest that apomorphine will disrupt escape learning, effects that appear to be correlated with the apomorphine-induced increase in motor activity.

Low doses of clonidine, an agent that inhibits NE, impairs habituation of activity. This investigator is also conducting experiments designed to lesion particular brain areas rich in dopaminergic terminals to observe the behavioral consequences of such lesions.

Development of the Central Nervous System

This part of the Developmental Neurology Branch (DNB) program supports mainly basic research in all aspects of normal and abnormal central nervous system (CNS) development. About half of the grants were for basic research on regulation of CNS growth and development; the remainder dealt with abnormal CNS development, neurogenesis, structure and organization, cell recognition, and genetics of the developing nervous system.

Regulation of normal CNS growth and development. This area is basic to understanding abnormal CNS development, and research in this area is vigorously supported by the DNB.

Tissue culture techniques are used to study the mechanisms that produce heterogeneity of cell types. In one study fluorescent markers were injected intracellularly to identify neuron precursors. In another, adrenergic and cholinergic markers were used to investigate regulatory processes in the sympathetic nervous system. The role of nerve growth factor, microfilaments and microtubules is studied in the formation of axonal processes, and efforts are being made to isolate and characterize the proteins tubulin and actin. The kinetics of these proteins and of myosin are intensively studied in order to elucidate the forces responsible for cytoplasmic streaming in growing neurons. Another study seeks to define the influences which control the development of neural crest cells into neurons. Apparently at the neural crest stage these cells are able to synthesize at least 5 neurotransmitter compounds, and later neuron specific enolase. Mechanisms of naturally occurring neuronal death are pursued by surgical and autoradiographic procedures. Results suggest that programmed neuronal death is related to removal of target cells.

A variety of other studies is concerned with regulation of growth and development of precerebellar nuclei, the spinocerebellar system, Mauthner neurons, the choroid plexus, superior colliculus and spinotectal system.

Abnormal development of the CNS. Several mouse mutants are used in investigations of developmental malformations of the CNS. Computer-assisted morphometry is used to study the cellular events which lead to malformation of neurons and axons, and of cortical structures of the Reeler mouse. The mechanisms of the teratogenic action of diethylstilbestrol (DES) on developing CNS is also being studied in mice. It is shown that there are DES receptors on the CNS as there are on organs of the urogenital system.

In a multidisciplinary program project, the ontogenesis of the central nervous system is disrupted by lesions and pharmacological methods, and the biological consequences of this disruption are studied to determine if there exists a critical time period during which a biochemical or physical insult has a significant effect on ontogeny, and the nature of adaptive responses on the part of the CNS.

In another study, histochemical and scanning EM methods are used to analyze the earliest stages in neural tube formation in the chick and newt. Initially, elongation of the primitive streaks and changes in cell shape take place; these are followed by elongation of the midline of the plate, and contraction of the microfilaments. Ultraviolet and concanavalin A application at these stages stop neural tube formation. These studies are expected to have potential clinical application in an area of vital interest to the DNB.

Neurogenesis. The time of origin of neurons is traced in several studies. By injecting ^{3}H-thymidine in pregnant rats it was found that the chronological order of neuron production in the upper and lower medulla, pons, and midbrain tegmentum is very precise. In the Rhesus monkey, it was observed that glial cells appear first in the brain stem and spinal cord, then in the diencephalon, telencephalon and cerebellum, thus these cells are present concomitantly with neurons in the early stages of development.

In other studies, use of antisera as specific surface markers for different types of neural cells has traced the origin of the auditory nuclei and VIII nerve projections, as well as the genesis of neuroaminergic projections to the brain and the establishment of their pathways from the brainstem.

Structure and organization. These studies utilize a variety of experimental animals and methods, and continue to enhance our knowledge of the morphology and ultrastructure of the nervous system. Among these are studies of brainstem projections to the cerebrum and cerebellum, neuronal and sympathetic organization of the cerebral cortex, and in-depth studies of Purkinje cells in the cerebellum, olfactory granule cells, and the acoustic nuclei.

Cell recognition. The powerful technique of development of monoclonal antibodies, is being used by several investigators to define molecules on the surface of neurons and muscle cells which allow for formation of specific connections during the development of the nervous system. Thus it has been shown that different types of cells exhibit specific binding sites for fibronectin, lectins and other specific proteins.

In other studies it was shown that dopaminergic neurons disassociated from one another associate selectively, i.e. association depends on the presence of appropriate dopamine target cells. The mechanics critical to neuroblast migration are also being studied in quail-chick transplants using ^{3}H-thymidine labelling.

Genetics. Animal models are a unique resource for many neuroscientists who are studying a large number of genetically determined neuromuscular disorders. DNB provides support for the development and propagation of mutant stocks of mice carrying, at latest count, 54 neurological mutants at 41 independent loci. These are being made available to interested laboratories.

In Drosophila, mutations which affect the nervous and muscular system are being studied as models for the analysis of interactions between nerve and muscle.

Other studies using the mouse, seek to define the code function of the vastly complex mammalian genome, particularly transcriptional and messenger RNA specificity during pre- and postnatal brain development. A mutant mouse defective for CNS myelination is being studied by tissue culture to gain insight into the cellular level of expression for this defect. Other mutants are used to study gene action in defects of Purkinje cells and disorganization of the cerebellar cortex.

Important advances have been made in supported research in transplantation of brain tissue. Transplanted embryonic brain tissue in rats will grow and differentiate and become integrated with the host, and establish connection within the brain. This potentially useful process in clinical research is apparently under genetic control because transplantation is successful between two strains of rats but not between two species.

Synapses. In the research area of synaptology more than 20 grants were active during this fiscal year within the DNB. These included a major long term program project concerned with the organization and development of neuronal systems in a variety of animal species with special emphasis on the morphology and physiology of synaptic interconnections. Another long term project involves the study of the factors that regulate growth and differentiation of neurons with special emphasis on the formation of appropriate synaptic interaction. Research efforts include the following: a study of the normal patterns of development of synaptic structures and the acute and chronic effects of lesions on these patterns at the electron microscopic level; studies on synaptic development both in vivo and in vitro in an original avian model of ciliary ganglion; a study of the precise sequence of events occurring during the formation of nerve muscle synapse; a study exploring the observation that adrenergic neurons in cell culture show cholinergic features at some stage of synaptic development. A promising new program project seeks to apply immunological, morphological and electrophysiological techniques to the problems of synapse development and function; a series of new, very creative experiments are underway to investigate acetylcholine receptors in a nerve-muscle tissue culture model in development of synapse; another new, original proposal seeks to discover which cell surface components are involved in the development of the nervous system, particularly in the establishment of specific synaptic connections; a new study will examine the phenomenon of the apparent "gathering in" of acetylcholine receptors into the synapse region as nerve-muscle contact develops; and a unique new study may provide information on the correlation between structural development and physiological behavior in the same cell during synaptic development.

III. NINCDS COLLABORATIVE PERINATAL PROJECT

Comprehensive Plan

The NINCDS Collaborative Perinatal Project (NCPP) is a longitudinal multidisciplinary research effort which seeks leads to the etiologies of cerebral palsy, mental retardation, learning disorders, congenital malformations, minimal brain dysfunction, convulsive disorders, visual abnormality, and communicative disorders through studies which relate the events, conditions, and abnormalities of pregnancy, labor and delivery to the neurological and mental status of the children of these pregnancies as the child grows and develops. Data collection is complete, and data analysis is now complete in almost all areas of study. The Comprehensive Plan for Analysis and Interpretation of Collaborative Perinatal Project Data provided the framework for this effort. The Comprehensive Plan included 10 primary and 10 secondary areas of study as listed below. The major emphasis of the project has shifted almost entirely to data interpretation and the writing of reports for publication of the NCPP research findings. Significant publications stemming from the Comprehensive Plan are noted in the listing below if the study area is concluded, in the individual contract narratives or project reports, and some are highlighted in the General Summary.

A. The ten primary areas are:

Cerebral Palsy (Project No. Z01 NS 02059-09 DNB)

Mental Retardation (Project No. Z01 NS 02106-08 DNB)

Communicative Disorders (Completed in FY'80 - See Lassman, F.M., Fisch, R.O., Vetter, D.K., and LaBenz, E.S.: Early Correlates of Speech, Language and Hearing. Edited by LaBenz, P.J., and LaBenz, E.S. Littleton, Massachusetts, PSG Publishing Company, 1980, 858 pp.) (Contract No. N01 NS 4-2326)

Visual Abnormality (Project No. Z01 NS 02107-08 DNB)

Convulsive Disorders (Project Nos. Z01 NS 02058-09 DNB &
Z01 NS 02234-06 DNB)

Learning Disorders (Project No. Z01 NS 02108-08 DNB)

Minimal Brain Dysfunction (Completed in FY'80 - See Nichols, P.L., and Chen, T.C.: Minimal Brain Dysfunction: A Prospective Study. Hillsdale, N.J., Lawrence Erlbaum Associates, 1981, 336 pp.) (Project No. Z01 NS 02062-09 DNB)

Congenital Malformations (Project No. Z01 NS 02109-08 DNB)

Birthweight-Gestational Age Relationships (Project No.
Z01 NS 02060-09 DNB)

Neuropathology, General Pathology and Placentology (Contract Nos.
N01-NS-3-2312 & N01-NS-7-2376)

B. The ten secondary areas are:

Toxemia (Completed in FY'77 - See Friedman, E.A., and Neff, R.K.: Pregnancy Hypertension. Littleton, Mass., PSG Publishing Co., Inc., 1977, 258 pp.)

Maternal Infection during Pregnancy (See report by Infectious Diseases Branch, NINCDS)

Neonatal Hyperbilirubinemia (Project No. Z01-NS-02112-08 DNB)

Maternal Anesthesia-analgesia during Labor and Delivery (Contract No. N01-NS-8-2381, and Project No. Z01 NS 02169-07 DNB)

Four-Year IQ (Completed in FY'75 - See Broman, S.H., Nichols, P.L, and Kennedy, W.A.: Preschool I.Q.: Prenatal and Early Developmental Correlates. Hillsdale, N.J., Lawrence Erlbaum Associates, distributor, Halsted Press, John Wiley & Sons, N. Y., 1975, 360 pp.)

Physical Growth and Development (Contract No. N01-NS-5-2308)

Twins (Project Nos. Z01 NS 02109-08 DNB and Z01 NS 02332-04 DNB)

Genetic and Socio-economic Factors (Project Z01 NS 01857-12 DNB)

Drugs taken during Pregnancy (Completed in FY'77 - See Heinonen, O.P., Slone, D., and Shapiro, S: Birth Defects and Drugs in Pregnancy. Littleton, Mass., Publishing Sciences Group, Inc., 1977, 516 pp.)

Labor and Delivery (Contract No. N01-NS-8-2381)

Summary of Work in Progress

Section on Cerebral Palsy and Other Motor Disorders

An edited monograph of the papers from the Consensus Development Conference on Febrile Seizures has gone to press. The Section Chief, Dr. Nelson, and Dr. Ellenberg, Office of Biometry and Field Studies, edited the monograph and contributed three chapters.

Many professional and lay journals published the panel report from this conference. An RFP went out, pursuant to the recommendations of the concensus panel, and responses will go to TMR in the near future. A number of invited presentations to professional groups have been made, centering in part on results of the consensus meeting.

A study is planned in Yugoslavia in pursuance of another of the panel recommendations. The section has also participated in establishment of a group to investigate time trends in CP incidence in the United States, in an effort to assess the results of changes in newborn care in this country.

In the cerebral palsy area, a univariate screen has been performed to evaluate maternal and pediatric conditions most strongly associated with cerebral palsy. Two of five regression analyses have been run and the third is imminent. Cerebral palsy at 7 years is found more frequently in boys than girls, and among whites than blacks. Twelve per cent of cerebral palsy is apparently caused by events occurring after the first month of life, most often infection or trauma. Clearly handicapping cerebral palsy was present at age 7 in 22-33/10,000 children, the range being related to race and sex. Studies have been completed and published demonstrating the relationship of birthweight and gestational age to cerebral palsy. Within each birthweight and gestational age group examined white males were at highest risk of cerebral palsy. Although low birthweight and immaturity are risk factors for cerebral palsy, 59% of cerebral palsy and 69% of the cerebral palsy other than spastic diplegia occurred in infants of term weight and full (37 or more weeks) gestational age.

Studies are now in press concerning low Apgar scores as predictors of long-term neurological morbidity, and early recognition of infants at "high-risk" for cerebral palsy. Associated handicaps have been investigated in children with cerebral palsy, and natural history described in children who "outgrew" cerebral palsy, i.e., those children who showed signs of cerebral palsy at an earlier age but at the 7-year examination were free of motor handicap. The major multivariate analyses relating to the antecedents of cerebral palsy are now in progress. Several analyses are underway to clarify associations revealed in the regression analyses.

In the convulsive disorders area, major findings are that approximately one in 20 children (57/1000) at age seven years have had at least one seizure. About 1/10 of that number (4.8/1000) had active epilepsy by the age of seven. In the NCPP population, epilepsy in childhood is approximately equal in prevalence in blacks and whites. Two-thirds of children who had seizures between one month and seven years of age had febrile seizures only. Data on prevalence of specific seizure disorders in early childhood are now available and were presented at an international meeting on child neurology. Approximately a quarter of children with epilepsy in early childhood have another major neurological handicap -- either mental retardation or cerebral palsy, or both. Seizures occurring in the first months of life were associated with a relatively high rate of death or subsequent disability including cerebral palsy. Neonatal seizures were found to be a major marker of risk for subsequent neurologic morbidity, and neonatal seizures in full term infants with very low Apgar scores appeared to be an important predictor of chronic neurologic disability. A manuscript on neonatal seizures in the NCPP has been prepared under contract. Low birthweight and short gestation were not important risk factors for seizure disorders in children who did not also have cerebral palsy. The major multivariate analyses concerning the antecedents of convulsive disorders are now in progress. Mothers with noneclamptic seizure disorders have been reported by others to be at increased risk for certain problems in their pregnancies or progeny. These associations and possible intermediary factors are being explored in the population of the NCPP.

A study of febrile seizures has been a major focus of the convulsive disorders area. Of 1706 children with febrile seizures followed to the age of 7 years, 2% had become epileptic by the age of 7 and another 1% had had at least one nonfebrile seizure not meeting the definition of epilepsy. Comparison of 431 children who have had febrile seizures only with their seizure-free siblings indicates that febrile seizures do not "cost" the child a loss in IQ or increased vulnerability to learning disorders. Three risk factors were identified which served to mark children at special risk of subsequent epilepsy among children who have had febrile seizures. The best predictor of recurrence of febrile seizures was early age of onset.

Current activities on febrile seizures include several invited presentations and chapters for books. An NIH Consensus Development Conference on Long-term Management of Children with Febrile Seizures was held last year. Results of the consensus meeting have been published in lay and professional journals, and the papers have been edited for a monograph, now in press. Results of the meeting are available in a DHHS publication Febrile Seizures, a National Institutes of Health Consensus Development Conference Summary, Vol. 3, No. 2. An RFP has been prepared for a study of cognitive and behavioral effects of anticonvulsant medication in children with febrile seizures, and responses will soon undergo Technical Merit Review. A study on EEG as a predictor in febrile seizures is planned to take place in Yugoslavia, and a survey has been prepared concerning medical management of febrile seizures.

Section on Mental Retardation and Learning Disorders

The Acting Section Chief, Sarah Broman, has been responsible for the administration of over 50 research grants in developmental neurology. The Section is developing a program announcement in the area of the neurophysiology of learning disorders encouraging research on measurement of brain electrical activity in well-defined subgroups of children with specific learning handicaps. The Section is also planning a workshop to discuss and reach some agreement on criteria for measuring and classifying learning disorders.

In the course of developing a research program on neurological aspects of learning disorders, Dr. Broman attended the meeting of the Scientific Studies Committee of the Association for Children with Learning Disabilities, met with the Deputy Director of NIH about the concerns of ACLD, and prepared a report on current PHS supported research on learning disorders. Dr. Broman has also participated in the scientific meetings of the Society for Research in Child Development, the American Psychological Association, and the Research Forum in preparation for the White House Conference for Children, Youth, and Parents.

In the mental retardation area, data analyses are completed, and a monograph is in preparation. The incidence of mild retardation, and to a lesser degree severe retardation, was inversely related to socioeconomic status. Classification of the severely retarded children shows that 25% of whites and 50% of blacks had no major genetic or neurological abnormality. Perinatal risk factors for the severely retarded group as a whole include Down's syndrome, major CNS malformations, neonatal seizures and clinical signs of perinatal hypoxia. For the subgroup of severely retarded with unknown etiology, perinatal risk factors include non-CNS malformations, peripheral nerve abnormalities, signs of hypoxia, and maternal urinary tract infection during pregnancy. Results of multivariate analyses of drugs taken during pregnancy showed that barbituates, non-barbituate anticonvulsants, and phenothiazines were associated with severe mental retardation among offspring in both ethnic groups. A chapter on selected risk factors for deficits in early cognitive development has been published.

In the learning disorders area, a monograph is to be submitted for outside review. The findings show that among children with at least average IQ but below average achievement test scores, socioeconomic status and family size were better predictors of unexpected school failure than were indices of physical or neurological status. Beginning in the preschool period, low achievers had higher frequencies of cognitive and behavorial problems, and neurological soft signs than did their IQ-matched controls. Hyperactive low achievers had an increased frequency of obstetrical complications. Sex differences were found in the predictors as well as in the incidence of unexpected academic failure. A summary of results has been published in a chapter on the methods and findings of the Collaborative Perinatal Project.

Analyses in the area of obstetric medication and later physical and cognitive development in a cohort of normal births are completed and a report is in preparation. The findings suggest that inhalants are independently associated with deficits in psychomotor and neuromotor functioning in infancy, and that some drugs given during labor and delivery are associated with lower scores on cognitive tasks at later ages.

The final report of the study of symptoms of minimal brain dysfunction was published in 1981. Learning difficulties were related to low socioeconomic status and tended to run in families; the familial association was likely determined environmentally. Preschool predictors were more strongly related to hyperkinetic-impulsive behavior than were early antecedents. Also implicated however, were genetics, demographic factors, pregnancy complications, and infant development. Both hyperkinetic-impulsive behavior and neurological soft signs were more highly related to preschool performance than to perinatal complications. Altogether more than 350 significant associations between the three MBD symptoms and antecedent variables were found. The identification of many of these antecedents, for example, frequent changes in residence, family configuration, maternal smoking, and specific physical abnormalities will be useful in the formation of etiological hypotheses and in programs of prevention and treatments.

Section on Birth Defects and Genetic Disorders

The Section Chief, N.C. Myrianthopoulos, has been responsible for the administration of over 60 research grants mainly in the area of developmental neurology. Among the new initiatives of the Section in this area has been the development of a program announcement for research related to the etiology, developmental embryology and natural history of neural tube defects.

Dr. Myrianthopoulos took an active part in the development of a neuroscience program in Greece, and in the assessment of preliminary data from the Italian Collaborative Perinatal Project. He also participated in the 12th World Congress of the World Federation of Neurology Research Group on Huntington's Chorea where he discussed with international scientists the state of the art, and research progress in this disease.

Dr. Myrianthopoulos also explored the possibility of utilizing the unique and large collection of early human abortuses available in Japan, in studies of neural tube defects.

Two parts of the 11-part program plan for the comprehensive analysis of NCPP data in the area of congenital malformations remain to be completed: the analysis of multiple malformations, and the analysis of the 7-year malformations. Though lack of computer programming help has slowed the pace of these analyses considerably, some progress has been made. Work on the analysis of multiple malformations has resumed and is continuing satisfactorily. Findings from the analysis of 7-year malformations indicate that 19% of children followed to age 7 years have malformations, representing an increase of 4% from 1 year, mainly due to newly identified eye, mouth and genitourinary malformations, and tumors. Over 70 new specific diagnoses have been made. Among these the most frequent are ocular hypertelorism, dental malformations, tumors, malformation syndromes, and chromosomal syndromes.

Epidemiologic and genetic analyses of neural tube defects have shown that the risk for these defects is related to the length of the interval between conceptions. An analysis of preconceptional and pregnancy maternal X-ray exposure has shown that the risk of childhood malignancies is 2.61 that of control when mothers were exposed to radiation before conception, and 2.59 when mothers were exposed during pregnancy.

Studies of twins are in progress to assess and interpret the influence of maternal, socioeconomic, neonatal, medical and other environmental factors on survival, growth and development, and on abnormal outcome of NCPP twins.

Section on Autism and Behavioral Disorders

Studies have continued on the 14 autistic children identified in the NCPP. Earlier published work on this sample reported increased vaginal bleeding during the second trimester of pregnancy. Cord blood samples have been examined for presence of certain antiviral antibodies but no significant results were found. Tabulations have been prepared on the autistic children and controls for a series of findings from the neonatal neurological examination, the 8-month developmental examination, and the 1-year neurological examination in an attempt to identify predictive signs of autism. Results indicate that no clinically useful signs were identified. The recruitment effort for the Section Head for the Autism and Behavioral Disorders Section continues.

Collaborative Perinatal Section

In the area of visual abnormality data analyses are complete and a final report was prepared and is undergoing revision.

The Birthweight-Gestational Age Relationships (Prematurity) analysis has been completed and a monograph is being prepared.

The two contracted analyses in the area of pathology, one for neuropathology and one for general and placental pathology are complete. In the neuropathology segment, a monograph report was received; editing of the manuscript continued during the fiscal year. In the general and placental pathology segment, work and reporting of results continued. A final, comprehensive report is expected.

A book describing the characteristics of NCPP children during their first year has been published. Hardy, J.B., Drage, J.S., and Jackson, E.C.: The First Year of Life. Baltimore, Md., The Johns Hopkins University Press, 1979, 336 pp.

Studies on neonatal hyperbilirubinemia as related to one year outcome have been published.

Work and reporting of results in the area of physical growth continued this fiscal year. A final comprehensive report is expected.

Support Functions

The Unit for Data Collection is responsible for maintaining the NINCDS Collaborative Project files and for the microfilming of the records in accordance with a system designed to facilitate data retrieval. During the fiscal year major efforts were concentrated on preparation of records for microfilming, editing microfilm, supplying records to DNB professional staff, outside investigators and consultants, providing research assistance to ongoing studies and preparing NINCDS microfilmed records for Federal Storage. Approximately 22,000 NCPP records were sent to the microfilm contractors and microfilm has been received for all records. Approximately 4,000 records have been sent to Federal Storage and an additional 27,000 are awaiting pickup for delivery to the Federal Records Center. Research assistance via computer tapes or microfilm records was provided to 16 investigators (7 in-house and 9 outside).

An RFP is planned to seek offers to produce a "Users Guide" to the NCPP data, with the expectation that, eventually, NCPP data files with appropriate documentation will be accepted by the National Archives.

The Unit for Production of Data Analysis has as its basic mission the processing and storage by digital computer of the medical research data collected by the NCPP. The major research files have been completed and in-depth statistical analysis has been performed.

The following systems are now in operation: (1) A financial system that accounts for all computer funds spent by the Branch; and (2) An automated bibliography of all NCPP publications.

An index of all Master File maternal variables has been completed. The creation of additional indices are under study.

A system to create an index of all variables found in the NCPP Master File, Variable File and Peripheral Files is under study.

Outside Requests for NCPP Data

It is still the policy of the DNB to encourage the appropriate use of the NCPP data by providing advice, data, and assistance to qualified biomedical and behavioral researchers who wish to utilize these data in their research. A policy statement has been developed which specifies the requirements to be met by a researcher who wishes to utilize NCPP data supplied by the DNB. The policy statement was formally approved by the Director, NINCDS and is available on request.

Requests for NCPP data to initiate new studies or to obtain specific information from NCPP data files continue to be received from researchers who receive their support from agencies and institutions other than the NINCDS. New, approved requests this fiscal year include:

Department of Hearing and Speech Sciences, University of Maryland, on Pre- and Perinatal Trauma, Handedness and Cognitive Abilities; Department of Pediatrics, U.C.L.A. School of Medicine, Harbor - U.C.L.A. Medical Center on Growth of Infants with rubella syndrome; Child Development Program, College of Physicians and Surgeons of Columbia University on the status, in Adolescence of children who have had neurological signs at age 7. Child Study Center, Brown University, on perinatal and early developmental characteristics of children who ultimately require special educational institutionalization because of mental retardation; Laboratory of Developmental Psychology, National Institute of Mental Health on psychobiological correlates of Behavior Problems in Children.

Highlights of Findings from the NCPP

Findings from the NCPP have and are continuing to have an impact on national health policy. It seems appropriate to highlight some of the more important contributions to date.

The concern over the potential dangers of alcohol consumption by a pregnant woman to her unborn fetus was highlighted in a notice in the Federal Register, Vol. 44, No. 29 - Friday, February 9, 1979. In that notice, the Department of the Treasury recommended a public awareness campaign to educate the public about the nature of the problem. The existence of the "fetal alcohol syndrome," a constellation of congenital anomalies thought to appear in offspring of chronic alcoholic women, was confirmed, prospectively, using data on women and children enrolled in the NCPP. The appearance of the paper in the Lancet (Jones, K.L., Smith, D.W., Streissguth, A.P., and Myrianthopoulos, N.C.: Outcome in offspring of chronic alcoholic women. Lancet I: 1076-1078, 1974) stimulated additional research and subsequent governmental and public concern over this issue.

The work by Dr. Dennis Slone and his colleagues at Boston University, completed under contract with the NINCDS, developed an association between cardiovascular birth defects and female hormones taken by the mother during pregnancy. The paper appearing in the New England Journal of Medicine (Heinonen, O.P., Slone, D., Monson, R.R., Hook, E.B., and Shapiro, S.: Cardiovascular birth defects and antenatal exposure to female sex hormones. N. Engl. J. Med. 296: 67-70, 1977) led directly to new Federal drug labeling requirements for this class of drugs as published in the Federal Register, Vol. 43, No. 199 on Friday, October 19, 1978. The paper is cited in the Federal Register.

Febrile seizures affect 3.5 percent of all children born in the United States. The study by Drs. Karin Nelson and Jonas Ellenberg, of the NINCDS, (Nelson, K.B and Ellenberg, J.H.: Prognosis in children with febrile seizures. Pediatrics 61: 720-727, 1978) presented data concerning the degree of risk of future epilepsy in children experiencing febrile seizures. In children with a prior neurological abnormality and one or more other risk factors (family history of epilepsy, first seizure type), the risk was high, but for children with no prior abnormality, no history of epilepsy in the immediate family, and when the first seizure was of a pure (not complex) type, the risk of subsequent epilepsy was quite low. This low risk group included 60% of children with febrile seizures and the authors state that this group would not seem an appropriate target population for chronic treatment aimed at the prevention of afebrile seizures. Another 34% of children had only one risk factor and they experienced little increase in risk of epilepsy. The NIH held a Consensus Development Conference which attempted to resolve the issue of management of febrile seizures in current medical practice. Findings from the NCPP were prominently featured in the final report emanating from the conference.

In 1979 a report of the Surgeon General on Smoking and Health was released. Chapter 8 is on Pregnancy and Infant Health and there are six references to publications from the NCPP that significantly contribute to the report's conclusion that smoking during pregnancy is deleterious to the baby during intrauterine life. In a June, 1981 publication (Garn, S.M., Johnston, M., Ridella, S.A., and Petzold, A.S.: Effect of Maternal Cigarette Smoking on Apgar Scores. Am. J. Dis. Child. 135: 503-506, 1981), it was reported that low and depressed Apgar scores in the newborn are related to the extent of maternal cigarette usage during pregnancy. At the two to three pack a day level there was a near quadrupling of low and depressed one and five minute scores. Apgar scores may be predictive of abnormal outcome in infants and children. This article was accompanied by a strong supporting editorial by Dr. T. Allen Merritt of the Departments of Pediatrics, Obstetrics and Gynecology, University of Rochester School of Medicine.

Children with learning difficulties, hyperactive behavior, and equivocal neurological signs have frequently been given the diagnosis of minimal brain dysfunction (MBD). In a book from the NCPP (Nichols, P.L. & Chen, T.C.: Minimal Brain Dysfunction: A Prospective Study, Hillsdale, N.J.: Lawrence Erlbaum Associates, 1981, 336 pp), the association among these three symptom areas was so slight that the existence of the syndrome is highly questionable.

Teenage pregnancy has been cited as a major health problem in the United States. In a study from the NCPP, risk factors associated with adolescent pregnancy were investigated within ethnic and socioeconomic subgroups (Broman, S.H.: Longterm Development of Children Born to Teenagers, in Scott, G., Field, T., and Robertson, E., (Eds.): Teenage Parents and Their Offspring, New York: Grune & Stratton, 1981, pp 195-224). The children of two age groups of adolescents were followed from gestation to age 7, and compared with children of mothers in their twenties. For most maternal and child characteristics examined, differences among the maternal age groups were smaller than those among socioeconomic or ethnic groups. Biological deficit was not strongly associated with early childbearing in this population, but the adverse effects of environmental deficit were evident in the lower cognitive and academic performance of children of teenagers.

Certain signs of neonatal neurologic dysfunction are predictive of chronic disability. (Nelson, K.B., and Ellenberg, J.H.: Neonatal Signs as Predictors of Cerebral Palsy. Pediatrics 64:(2), 1979). The risk of CP was increased by 10 to 33-fold in babies born weighing less than 2000 gm, or with heads that were very small for their birthweights. Poor activity, weak cry and suck, unstable body temperature, and stiffness or floppiness of muscle tone were also signs of trouble. Even more ominous, with more than 50-fold increases of risk, were neonatal seizures or Apgar scores of 3 or less at ten minutes or later. These characteristics were also markers of considerable risk of early death. For 0.5% of surviving infants an overall impression of abnormality of brain function during the nursery period was recorded by the attending physician; there was a 99-fold increase in CP among these children. It was thus possible to recognize newborn infants who were in special danger of long-term handicap. Early recognition of such infants can lead to exploration of factors in pregnancy, and labor and delivery that might have contributed to the poor condition of the infants, the aim being to develop better means of prevention of such problems. In addition, identification of babies at special risk may aid development of new treatment methods for the care of these babies.

There has been a great deal of attention to the increase of risk of cerebral palsy in low birthweight, and it is true that low birthweight and short gestation, were important risk factors for CP. However, low birthweight and short gestation, especially of degree sufficient to relate strongly to CP, are uncommon. The majority of children with CP were of normal birthweight and term gestational age. (Ellenberg, J.H., and Nelson, K.B.: Birth weight and gestational age in children with cerebral palsy or seizure disorders. Am. J. Dis. Child. 133:1044-1048, 1979). Preterm children with CP by age 7 years tended to have been even smaller at birth, than was appropriate for their short gestations. Low birthweight, preterm birth, and smallness for dates at term were significantly related to the risk of seizure disorders in children free of CP.

Other significant findings from the NCPP include evidence that there is prior neonatal brain dysfunction in sudden infant death syndrome (Naeye, R.L., Ladis, B., and Drage, J.S.: Sudden infant death syndrome: a prospective study. Am. J. Dis. Child. 130: 1207-1210, 1976), that only one third of congenital malformations are detected at birth (Myrianthopoulos, N.C. and Chung, C.S.: Congenital malformations in singletons. Epidemiologic survey. Report from the Collaborative Perinatal Project. Birth Defects, Orig. Art. Series, Vol. X, No. 11, 1974), that bilirubin is neurotoxic at intermediate levels (Scheidt, P.C., Mellits, E.D., Hardy, J.B., Drage, J.S., and Boggs, T.R.: Toxicity to bilirubin in neonates: infant development during the first year in relation to maximum neonatal serum bilirubin concentration. J. Pediatr. 91: 212-297, 1977.), and that frequency of coitus during pregnancy may be implicated in the etiology of amniotic fluid infections. (Naeye, R.L.: Coitus and associated amniotic-fluid infections. N. Engl. J. Med. 301: 1198-1200, 1979.)

IV. ADDITIONAL ACTIVITIES

The Office of the Chief, DNB, continues as the NINCDS focal point for implementation of the Privacy Act. The Chief, DNB, continues to serve as NINCDS Privacy Act Coordinator. Activities for this fiscal year include the following: (1) advice to NINCDS personnel regarding Privacy matters; (2) determination of the applicability of the Privacy Act to each new NINCDS contract involving human subjects; (3) required quarterly and annual reports prepared and submitted to the NIH Privacy Act Coordinator; (4) reviewing requests for access to or amendment of grant records; (5) attending orientation sessions regarding changing regulations in implementation of the Act; and (6) revising NINCDS System Notices to comply with new regulations.

The Office of the Chief, DNB, continues to administer the Clinical Research Panel, NINCDS Contract Review for the Protection of Human Subjects, and the Chief, DNB, serves as Chairman. This panel has the responsibility for reviewing NINCDS contracts for adherence to DHHS and NIH rules and regulations regarding the protection of human subjects in research and recommending approval or disapproval to the Director, NINCDS. During the first nine months of the fiscal year, 4 new contract proposals were reviewed by the Panel, and 13 renewals were processed.

The Chief, DNB, and the Staff Assistant to the Chief, DNB, are members of the NIH Contract Compliance Committee for Project Officers, chaired by the Contract Compliance Coordinator, NIH. This committee had as its charge the development of a questionnaire to be administered by project officers to principal investigators/project directors on NIH contracts for the purpose of increasing awareness of and monitoring compliance with Federal requirements for Equal Employment Opportunity. During last fiscal year a pilot course for NIH Project Officers was developed and tested and formal training initiated NIH wide, and use of the questionnaire, in the field, commenced. The committee continues to advise the NIH Contract Compliance Coordinator concerning this program as various issues arise and reports are drafted.

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1980 through September 30, 1981

CHILDREN'S HOSPITAL MEDICAL CENTER, BOSTON, MASSACHUSETTS (N01-NS-3-2312)

Title: Combined Neuropathologic and Epidemiologic Study

Contractor's Project Director: Floyd H. Gilles, M.D.

Current Annual Level: $ 0.00

Objectives: The contract has analyzed the neuropathology collection of the NINCDS Collaborative Perinatal Project (NCPP). An estimate of the quality of the material and a catalogue of gross brain abnormalities has been prepared. Plots of fetal brain weight of grossly normal brains against estimated gestational age, utilizing a Gompertz function, were made and an analysis completed relating events of pregnancy, labor, and delivery. A comparison was made of rate of brain weight acquisition in utero to rate of brain weight acquisition after birth as a function of total (gestational plus survival) age. A study was made of intracranial hemorrhage including topography of hemorrhage. Risk factors associated with perinatal telencephalic leucoencephalopathy were studied. A cerebral necrosis study included criteria of necrosis in the perinatal brain, and an evalution of selected risk factors in relation to subclassification of neuronal and white matter necrosis.

Major Findings: Review and classification of pathology material are complete. Data analysis is complete and a 23-chapter monograph has been prepared and has received outside review.

Course of Contract: June 1, 1973 through December 31, 1976. The contract is terminated; extra time is being allowed to complete and publish the monograph report.

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1980 through September 30, 1981

UNIVERSITY OF MICHIGAN (NO1 NS 5-2308)

TITLE: Physical Growth Analysis

Contractor's Project Director: Stanley M. Garn, Ph.D.

Current Annual Level: $ 00.00

Objectives: To develop the physical growth measurement data on the 50,000 children examined within the framework of the NINCDS Collaborative Perinatal Project (NCPP). Specifically:

1. Develop for body weight, length, chest circumference and head circumference, a set of tabular, percentile, normative tables of (a) size-for-age, (b) increments of size for age-interval, (c) size-for-size for age and size for gestation length for whites, blacks and Puerto Ricans separately and for boys and girls separately. This set of tables is largely intended as a reference document for the NINCDS Collaborative Perinatal Project.

2. Develop a set of summary tabulations and reports, directed to the major pediatric and growth-related users, complete with narrative and graphs, with the purpose of providing in the professional literature both an account of major substantive findings, and an in-the-literature account of the major data.

3. To correlate the incidence and prevalence of dental and facial abnormalities with neurological defects, congenital abnormalities and other disorders of childhood.

Major Findings: The tables, with accompanying graphs, as outlined in 1., above, are complete. Findings are reflected in approximately 20 publications to date.

Significance to the Program: The findings are important to the pediatric community as well as to physical anthropologists and nutritionists in that they represent results from the largest longitudinal data base yet studied in the U.S.

Course of Contract: Terminated April 30, 1980. Dr. Garn continues to analyze and publish NCPP data with support from sources other than the NINCDS. The planned series of publications is being completed and a final, comprehensive report has been requested.

Publications:

Garn, S.M., Cole, P.E., and Bailey, S.M.: Living together as a factor in family-line resemblances. Hum. Biol: 51:565-587, 1979.

Garn, S.M., Petzold, A.S., Ridella, S.A., and Johnston, M.: Effect of smoking during pregnancy on Apgar and Bayley scores. The Lancet II: 912-913, 1980.

Garn, S.M.: Continuities and change in maturational timing. In Grim, O.G., and Kagan, J. (Eds.): *Constancy and Change in Human Development*, Cambridge, Harvard University Press, 1980.

Garn, S.M.: Human growth. *Ann. Rev. Anthropol*. 9:275-279, 1980.

Garn, S.M., Ridella, S.A., Petzold, A.S., and Falkner, F.: Maternal hematologic levels and pregnancy outcomes. *Seminars in Perinatology* 5(2):155-162, 1981.

Garn, S.M., Johnston, M., Ridella, S.A., and Petzold, A.S.: Effect of maternal cigarette smoking on Apgar scores. *Am. J. Dis. Child*. 135:503-506, 1981.

Garn, S.M.: Lower hematocrit levels in blacks are not due to diet or socioeconomic factors. *Pediatrics* 67:580, 1981.

Garn, S.M., Keating, M.T., and Falkner, F.: Hematologic status and pregnancy outcomes. *Am. J. Clin. Nutr*. 34:115-117, 1981.

Lamb, M.E., Garn, S.M., and Keating, M.T.: Correlations between sociability and cognitive performance among eight-month olds. *Child Dev*. 52:711-713, 1981.

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1980 through September 30, 1981

THE PENNSYLVANIA STATE UNIVERSITY, UNIVERSITY PARK, PA. (N01-NS-7-2376)

Title: Analysis of General and Placental Pathology Data

Contractor's Project Director: Richard L. Naeye, M.D.

Current Annual level: $ 0.00

Objectives: The objectives of the last extension of the contract were (1) to complete the determination of the effects of smoking on the fetus, (2) a further explanation of the relationship between prepregnancy weight for height and placental growth as related to fetal growth and pregnancy outcome, and (3) a determination if selected factors thus far examined have an independent influence on long term psychomotor development in NCPP children.

Major Findings: Findings are reflected in approximately 43 publications to date.

Course of Contract: The contract terminated July 31, 1979; extra time is allowed to complete the planned series of publications, and a final, comprehensive, report is expected. Dr. Naeye continues to analyze and publish NCPP data with support from an NINCDS grant (1 R01 NS 16403-01).

Publications:

Naeye, R.L: The outcome of diabetic pregnancies: a prospective study. In Pregnancy Metabolism, Diabetes and The Fetus, Ciba Foundation Symposium 63 (new series), Amsterdam, 1979, Excerpta Medica, pp 227-241.

Naeye, R.L.: Sudden infant death. Sci. Am. 242:52-58, 1980.

Merrit, T.A., Lawrence, R.A., and Naeye, R.L.: The infants of adolescent mothers. Pediatr. Ann. 9:32-49, 1980.

Naeye, R.L.: Abruptio placentae and placenta previa: frequency, perinatal mortality and cigarette smoking. Obstet. Gynecol. 55:701-704, 1980.

Naeye, R.L.: Factors in the mother/infant dyad that influence the development of infections before and after birth. In Perinatal Infections, Ciba Foundation Symposium 77 (new series), Amsterdam, 1980, Excerpta Medica, pp 3-16.

Naeye, R.L.: Effects of maternal nutrition on the outcome of pregnancy, obstetrical decisions and neonatal outcome. Proceedings of the 78th Ross Conference on Pediatric Research, Columbus, Ohio, Ross Laboratories, 1980, pp 17-25.

Naeye, R.L.: Effects of maternal nutrition on the outcome of pregnancy. In Porter, I.H. and Hook, E.B. (Eds.): Human Embryonic and Fetal Death. New York, Academic Press, 1980, pp 197-206.

Naeye, R.L.: Cigarette smoking and pregnancy weight gain. (Letters to the Editor) The Lancet I:765-766, 1980.

Naeye, R.L.: Influence of maternal cigarette smoking during pregnancy on fetal and childhood growth. Obstet. Gynecol. 57:18-21, 1981.

Naeye, R.L.: Teenaged and pre-teenaged pregnancies: consequences of the fetal-maternal competition for nutrients. Pediatrics 67:146-150, 1981.

Naeye, R.L., and Chez, R.: Effects of maternal acetonuria and low pregnancy weight gain on children's psychomotor development. Am. J. Obstet. Gynecol. 139:189-193, 1981.

Naeye, R.L.: Maternal nutrition and pregnancy outcome. In Dobbing, J. (Ed.): Maternal Nutrition in Pregnancy, Eating for Two? London, Academic Press, 1981, pp 89-111.

Naeye, R.L.: Nutritional/nonnutritional interactions that affect the outcome of pregnancy. Am. J. Clin. Nutr. 34:727-737, 1981.

Naeye, R.L., Kissane, J.M., and Kaufman, N.: Perinatal Diseases. Baltimore, Williams & Wilkins, 1981.

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1980 through September 30, 1981

CHILDREN'S HOSPITAL MEDICAL CENTER, BOSTON, MASSACHUSETTS: (N01-NS-7-2377)

TITLE: A Prospective Cohort Epidemiologic Study of Learning Handicaps in Children Attending School

Contractor's Project Director: Alan Leviton, M.D.

Current Annual Level: $12,194 (1.5 months of FY 81)

Objectives: Conduct analyses of antecedents of school behavior and school achievement at age 9 in an identified sample of children in the Boston component of the NINCDS Collaborative Perinatal Project (NCPP) for the purpose of identifying risk factors for learning disorders.

Major Findings: Five learning handicaps in boys and six in girls have been identified as outcomes of interest. Antecedents are being analysed by epoch--e.g.--pre-pregnancy, pregnancy, delivery, early postnatal. An interactive multiple logistic regression procedure is being used to analyse the data. Risk factors for learning handicaps include low family income, large family size, prior abortions, and some complications of pregnancy.

Course of Contract: The contract which began on September 30, 1977 terminated November 14, 1980. Additional time has been allowed for completion of a monograph.

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1980 through September 30, 1981

BETH ISRAEL HOSPITAL, BOSTON, MASSACHUSETTS (N01-NS-8-2381)

Title: Comprehensive Study of Labor and Delivery Effects on Offspring

Contractor's Project Director: Emanuel A. Friedman, M.D.

Current Annual Level: FY-81 funds: $199,617.00

Objectives: The objectives are (1) to determine the effects on the fetus and the surviving infant of clinically definable labor factors, labor disorders and the spectrum of delivery procedures, and thus to identify and quantitate the specific risk factors in labor and delivery that contribute to perinatal mortality and to the development of long-term neurological and developmental disorders in children, and (2) to determine relationships between the various types of maternal anesthesia-analgesia and development of the child; specifically, to examine in detail the time-dose relationships and drugs used in combination during the course of labor and delivery, in relation to long-term neurological outcome in the child.

Major Findings: Work on the contract has progressed and the required report following Phase 8 has been received. The analysis of cases with arrest disorders has been completed. Computer programs capable of identifying cases with either arrest of dilatation or arrest of descent (or both) were developed. These algorithms, when applied to the entire NCPP data bank, yielded 833 nulliparas and 945 multiparas with arrest of dilatation (10.5% and 14.7% of the respective populations) plus 1,535 nulliparas and 681 multiparas with arrest of descent (19.4% and 10.6%, respectively, of their base populations). It was clearly understood that many--if not most--of these cases represented normal variants in which the duration of the arrest was very short (even artifactual perhaps) with little relevance to the patient, to her labor, or to fetal outcome.

In order to resolve this issue--that is, to determine how long a duration arrest had to persist before it could be considered meaningful in terms of its potential impact--we studied the range of outcomes for infants delivered of women with arrest disorders according to the duration of the arrest. Patients were stratified according to the duration of either form of arrest in 15 minute increments. Outcomes were ascertained and the relative rates calculated for such important measures of results as stillbirth, neonatal death, five-minute Apgar score depression, abnormal 8-month Bayley mental, motor, and global scores, 1-year neurological examination, and 4-year intelligence quotient. In general, the longer the duration of arrest, the greater the adverse effect. This was not unexpected, of course, but the data permitted us to ascertain a practical cutpoint for purposes of defining the criterion for diagnosing a clinically significant arrest disorder. Clinical significance in this context (one of the objectives of this investigation) refers to the adverse impact on the fetus/infant.

Course of Contract: March 13, 1978 through March 12, 1982. A fourth and final contract year has been awarded.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 01857 - 12 DNB

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

The Genetics of Intellectual and Motor Performance

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Sarah H. Broman	Acting Chief, MRLDS	DNB NINCDS
Other:	Paul L. Nichols	Research Psychologist	DNB NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Developmental Neurology Branch

SECTION
Mental Retardation and Learning Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Familial influences on tests of mental and motor performance at ages eight months and four and seven years were examined by comparing correlation coefficients among monozygotic twins, dizygotic twins, full siblings, half siblings, and cousins within race, sex, and social class groups. A paper has been published on familial resemblance in infant mental development. The correlations between scores of twin and sibling pairs on the Stanford-Binet (age 4) and Wechsler (age 7) intelligence tests suggested a greater genetic influence than was found for infant test scores. Correlation between scores of half-siblings, rarely reported, were consistent with predictions from a polygenic model of inheritance of intelligence. An investigation of relatives of children with IQs in the retarded range suggested genetic influences on the etiology of mild retardation among whites but not among blacks. This project is now terminated.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02058-09 DNB

PERIOD COVERED
October 1, 1980 Through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Convulsive Disorders Data Analysis Group

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K.B. Nelson	Pediatric Neurologist	DNB NINCDS
PI:	J.H. Ellenberg	Mathematical Statistician	OBFS NINCDS
PI:	D.G. Hirtz	Expert Consultant	DNB NINCDS

COOPERATING UNITS (if any)

Dr. J. Freeman, Johns Hopkins
Dr. K. Holden, Johns Hopkins

LAB/BRANCH
Developmental Neurology Branch

SECTION
Section on Cerebral Palsy and Other Motor Disorders

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.9	PROFESSIONAL: 0.6	OTHER: 0.3

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study examines the relationship between perinatal factors and the occurrence of seizure disorders in childhood in a large, prospectively studied population. In addition to the central question of etiology, it investigates frequency, prognosis, demographic characteristics, and a number of other aspects of these disorders. Univariate screen of maternal, obstetric, and pediatric risk factors, and demographic analysis, have been completed. File creation for multivariate analysis is now complete, and regression analyses are in progress. Selected topics of particular clinical relevance are under examination.

Project Description: Project No. Z01 NS 02058-09 DNB

Objectives: To examine maternal characteristics, conditions of pregnancy, labor, delivery and the neonatal period, and illness and injuries of early childhood for their association with seizure disorders. To seek clinically useful indices for prediction, to evaluate clustering of other handicaps with convulsive disorders, and to examine the frequency of seizure disorders in the population of the NINCDS Collaborative Perinatal Project.

Methodology: The preliminary program to screen antecedent obstetric variables and early clinical manifestations with regard to their association with seizure disorder diagnoses has been completed. The analysis of demographic factors (e.g., institution, race, socioeconomic status, etc.) and their impact on the incidence and risk of seizure disorders is now available, and is in the process of assessment. A study into the natural history of seizure disorders from one to seven years of life is underway, taking full advantage of the prospective nature of the NINCDS Collaborative Perinatal Project.

Drs. Freeman and Holden have completed a study of the prognosis of neonatal seizures, and have presented some of their findings at an international meeting. Their manuscript has been submitted for publication.

Major Findings: Approximately one in twenty children (57/1000) followed to the age of seven years had at least one seizure. About one-tenth that number (4.8/1000) had active epilepsy by the age of seven. As studied in the NINCDS Collaborative Perinatal Project, active epilepsy in childhood is slightly more common in girls than boys, and approximately equal in rate in whites and blacks.

A major substudy on febrile seizures (Z01 NS 02234-06 DNB) is described separately. A number of reports, letters, and invited chapters have been published. It is proposed to followup these studies with a survey to establish current practice with regard to the management of febrile seizures by the various medical subspecialties. A consensus meeting has been held concerning questions of longterm management of children with febrile seizures.

Data on the prevalence of specific seizure disorders in early childhood are now available. A presentation on this subject was made to an international child neurology meeting, and a manuscript is in preparation.

Approximately a quarter of children with epilepsy in early childhood have another major neurological handicap: mental retardation or cerebral palsy, or both. The other three-quarters of epileptic children did not have these additional disabilities. Analysis of the antecedents and clinical course in these two major groups is in progress.

Seizures occurring in the first month of life were associated with a relatively high rate of death or subsequent disability, including cerebral palsy. Neonatal seizures are a major marker of risk for subsequent neurologic morbidity. A manuscript has been prepared by investigators at Johns Hopkins, under contract, and has been submitted for publication.

Project Description:

A report has been published concerning birthweight and gestational age as risk factors for seizure disorders. Low birthweight, immaturity and smallness for dates at term were not important antecedents of epilepsy in children free of cerebral palsy. Maternal, obstetrical, and early childhood characteristics which are associated with seizure disorders are now under study. A paper on chance of recurrence following an initial nonfebrile seizure is in preparation.

Future Course: Demographic data on convulsive disorders in Study children, and the univariate screen of antecedent maternal and pediatric characteristics are now complete. Multivariate analysis has begun. Selected topics of particular medical importance are being examined in sub-studies. A monograph on convulsive disorders in childhood will be prepared.

Significance: The convulsive disorders are a common and socially costly medical problem. It is estimated that about 4 million Americans have some form of epilepsy. The cost of the epilepsies in direct payments and medical expenses has been calculated at more than $4 billion per year. The information generated in the NINCDS Collaborative Perinatal Project may contribute useful information in this important problem area.

Publications:
See Febrile Seizures.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02059-09 DNB

PERIOD COVERED

October 1, 1980 Through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Cerebral Palsy Data Analysis Group

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: K.B. Nelson	Pediatric Neurologist	DNB NINCDS
PI: J.H. Ellenberg	Mathematical Statistician	OBFS NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Developmental Neurology Branch

SECTION

Section on Cerebral Palsy and Other Motor Disorders

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.2	PROFESSIONAL: 0.8	OTHER: 0.4

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This large prospective study attempts to add to available knowledge of the perinatal factors associated with motor handicaps in childhood, the primary goal being to identify areas for possible preventive efforts.

Studies on the prevalence, on perinatal factors and neonatal signs in the early recognition of cerebral palsy have been published. Data on demographic analysis and a univariate screen of maternal and pediatric factors associated with cerebral palsy are available. Multivariate analysis is nearing completion.

PHS-6040
(Rev. 2-81)

Project Description: Project No. Z01 NS 02059-09 DNB

Objectives: To examine the etiology of motor disabilities in children, to improve clinical prediction, and to examine the relative frequencies of motor and associated disabilities in the population of the NINCDS Collaborative Perinatal Project.

Methodology: The univariate screen relating antecedent obstetric variables and early clinical manifestations with regard to their association with cerebral palsy diagnoses has been completed and multivariate analyses are in progress. The analysis of demographic factors (e.g., institution, race, socioeconomic status, etc.) and their impact on the incidence and risk of cerebral palsy is available. Study of the natural history of cerebral palsy from one to seven years of life has been performed, taking advantage of the prospective nature of the NINCDS Collaborative Perinatal Project.

Future Course: The multivariate analysis of the obstetric, early clinical and demographic factors is under way.

Major Findings: Cerebral palsy at seven years is somewhat more frequent in boys than girls, and among whites than blacks. Twelve per cent of cerebral palsy is apparently caused by events occurring after the first month of life, most often infection or trauma.

Clearly handicapping cerebral palsy was present at age seven in 22-33/10,000 children, the range being related to race and sex. Within each birthweight and gestational age group examined, white males were at highest risk of cerebral palsy.

A listing of maternal and pediatric conditions most strongly associated with cerebral palsy outcomes has been made, and is the basis for multivariate analysis.

Studies have been completed concerning:

1. The relationship of birthweight and gestational age to cerebral palsy (CP). Although low birthweight and immaturity are risk factors for CP, 59% of CP and 69% of CP other than spastic diplegia, occurred in infants of term weight and full 37 or more weeks gestational age. Preterm infants with later CP tended to be undergrown even considering their short gestations.

2. Signs of neonatal neurologic dysfunction as predictors of CP. Certain signs on neonatal neurological examinations, and observations in the newborn nursery, are strongly associated with the likelihood of later CP. This study permits evaluation of the potential utility of neonatal mass screening programs for motor deficits.

3. Signs on examination of four month old infants in the early recognition of CP. The potential utility of separating young infants by level of risk of CP has been documented. Paper in press.

4. Apgar scores as predictors of longterm neurologic morbidity. Very low Apgar scores at ten, 15 and 20 minutes identify surviving babies at high risk for CP, which in this circumstance is usually accompanied by severe mental retardation and often by seizure disorders. Defects of hearing and speech may be present in children who escape CP after severe asphyxiated injury. Mild or brief exposure to asphyxia is not accompanied by much increase in risk of chronic neurologic morbidity. Paper in press.

Studies are now in manuscript form concerning:

1. Associated handicap in children with CP. In addition to motor disability, children with CP have an increased frequency of intellectual, sensory and behavioral disorders, and seizure disorders. This study quantifies the degree of the association of CP with other handicaps, according to severity of CP and to specific CP type.

2. Children who "outgrew" CP. Subjects who were free of CP at seven years were more likely to be mentally retarded, to have nonfebrile convulsions, speech articulation problems, and other disabilities if they had shown abnormal motor signs on examination at one year of age. Children with documented early motor abnormalities, especially those of mild degree, may be free of motor handicaps by early school age but at risk for other disabilities.

Significance: Approximately 750,000 persons in the United States are victims of cerebral palsy; milder forms of cerebral palsy are more frequent still. The loss in social and economic terms is immense, and individuals with CP are often lifelong dependents of their families or the state. Our aims are to identify areas in which preventive efforts may be effectively directed, to improve clinical prognostication, to examine clustering of handicaps, and to estimate relative frequency of cerebral palsy conditions.

Publications:

Nelson, K.B. and Ellenberg, J.H.: Apgar scores as predictors of chronic neurologic disability. Pediatrics 68:36-44, 1981.

Ellenberg, J.H. and Nelson, K.B.: Early recognition of infants at high risk of cerebral palsy: examination at age four months. Dev. Med. Child Neurol., in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02060-09 DNB

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Birthweight-Gestational Age

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J. S. Drage	Chief	DNB, NINCDS

COOPERATING UNITS (if any)
J. B. Hardy, The Johns Hopkins University
E. D. Mellits, The Johns Hopkins University

LAB/BRANCH
Developmental Neurology Branch

SECTION
Collaborative Perinatal Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.10	0.05	0.05

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The final analyses, including a rerun of parts of Phase II and all of Phase III have been completed. Phase II, a multivariate analysis to determine relationships with birthweight, included analyses of primigravida only, as well as all gravida. Analyses were run utilizing information prior to delivery and separately at delivery (for example, placenta weight). Phase III examines events subsequent to birth as a function of information available at birth. These results are summarized in the form of Empirical Risk Tables which describe the empirical probability of the negative outcomes within the first year of life as a function of birthweight, gestational age, race, sex and placenta weight. The structure of the manuscript has been formed into four sections: 1. Description, 2. Concomitant Events, 3. Antecedents, 4. Subsequent Risk. Emphasis for the text material over the past year has been on finalizing figures and tables. Virtually all are completed. The writing of the monograph is in progress and is scheduled for completion in December, 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02062 - 09 DNB

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Minimal Brain Dysfunction

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P. L. Nichols	Research Psychologist	DNB NINCDS
Other:	Ta-Chuan Chen	Sr. Math. Statistician	OBFS NINCDS

COOPERATING UNITS (if any)

OBFS, OD, NINCDS

LAB/BRANCH
Developmental Neurology Branch, NDP

SECTION
Mental Retardation and Learning Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .01	PROFESSIONAL: .01	OTHER: .00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Antecedents of minimal brain dysfunction were investigated by examining the association of three major symptoms--learning difficulties, hyperkinetic-impulsive behavior, and neurological soft signs--with socioeconomic, perinatal, developmental, and familial variables. A major report describing the project was published in 1981. Learning difficulties were related to low socioeconomic status and tended to run in families; the familial association was likely determined environmentally. Preschool predictors were more strongly related to hyperkinetic-impulsive behavior than were early antecedents. Also implicated,however, were genetics, demographic factors, pregnancy complications, and infant development. Both hyperkinetic-impulsive behavior and neurological soft signs were more highly related to preschool performance than to perinatal complications. Altogether more than 350 significant associations between the three MBD symptoms and antecedent variables were found. The identification of many of these antecedents, for example, family configuration, maternal smoking, and specific physical abnormalities will be useful in the formation of etiological hypotheses and in programs of prevention and treatments.

PHS-6040
(Rev. 2-81)

Publications: Nichols, P.L. and Chen, T.C.: Minimal Brain Dysfunction: A Prospective Study. Hillsdale, N.J.: Lawrence Erlbaum Associates, 1981, 336 pp.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02106 - 08 DNB

PERIOD COVERED

October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Developmental Factors Associated with Mental Retardation

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S. H. Broman	Acting Chief, MRLDS	DNB NINCDS
Other:	P. L. Nichols	Research Psychologist	DNB NINCDS
	J. P. Pomeroy	Systems Analyst	DNB NINCDS

COOPERATING UNITS (if any)

Dr. Peter Shaughnessy, University of Colorado Medical Center
Dr. Wallace Kennedy, Florida State University

LAB/BRANCH

Developmental Neurology Branch

SECTION

Mental Retardation and Learning Disorders Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.7	.5	.2

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to identify predictors of mental retardation in a population of 37,000 children followed from the prenatal period to age 7. The incidence of mild retardation (1% in whites and 5% in blacks) and to a lesser degree, of severe retardation (0.5%) was inversely related to socioeconomic status. Among the severely retarded, 25% of whites and 50% of blacks had no major genetic or neurological abnormality. Perinatal risk factors for the severely retarded group as a whole include Down's syndrome, major CNS malformations, neonatal seizures and clinical signs of perinatal hypoxia. For the subgroup of severely retarded with unknown etiology, perinatal risk factors include non-CNS malformations, peripheral nerve abnormalities, signs of hypoxia, and maternal urinary tract infection during pregnancy. Results of multivariate analyses of drugs taken during pregnancy showed that barbiturates non-barbituate anticonvulsants, and phenothiazines were associated with severe mental retardation in the offspring in both ethnic groups. A report on selected risk factors for deficits in early cognitive development is in press. This study is completed and a monograph is in preparation.

PHS-6040
(Rev. 2-81)

Publications: Broman, S.H. Risk factors for deficits in early cognitive development. In G. Berg & H. Maillie (Eds.): Measurement of Risks. New York: Plenum Press, in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02107-08 DNB

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)
The Study of Visual Abnormalities in the NINCDS Collaborative Perinatal Project

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: R. Feinberg	Research Psychologist (retired)	DNB, NINCDS

COOPERATING UNITS (if any) W.R. Baldwin, New England College of Optometry; R.E. Hoover, Baltimore, Md.; R.P. Kling, Georgetown Univ. Hosp.; M.A. Whitcomb, Nat. Acad. of Sc.; S.Z. Wood, Washington, D.C.; F.A. Young, Wash. State Univ.

LAB/BRANCH
Developmental Neurology Branch

SECTION
Collaborative Perinatal Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0.0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project includes the analysis between visual abnormalities in NCPP children and predictor variables; anecdotal treatment based on case histories of unusual visual abnormalities; special studies of high-incidence disorders; case studies of the blind children; and, preparation of a monograph encompassing these subjects. Basic data analysis is complete and a draft manuscript of the findings was prepared and is currently being revised.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02108 - 08 DNB

PERIOD COVERED
October 1, 1980 through Sepember 30, 1981

TITLE OF PROJECT (80 characters or less)

Developmental Factors Associated with Learning Disorders

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S. H. Broman	Acting Chief, MRLDS	DNB NINCDS
Other:	E. C. Bien	Research Psychologist	DNB NINCDS
	J. D. Pomeroy	Systems Analyst	DNB NINCDS

COOPERATING UNITS (if any)

Dr. Peter Shaughnessy, University of Colorado Medical Center

LAB/BRANCH
Developmental Neurology Branch

SECTION
Mental Retardation and Learning Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .7	PROFESSIONAL: .5	OTHER: .2

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study identified early behavioral, physical and family characteristics of children with average IQ scores and below average school achievement, approximately 3% of the NCPP population. Low achievers were compared with their IQ-matched academically successful controls on prospectively ascertained indices of cognitive and physical development and family environment. Cognitive deficits and behavioral problems in the preschool period were associated with low achievement at age 7. Socioeconomic status (SES) and family structure were better predictors of low achievement than were indices of physical development or medical status. Low achievers were born into low SES, large families, and two-thirds of them were boys. As preschoolers, they had more language difficulties and lower IQ scores than controls. At age 7, deviant behavior, verbal and non-verbal cognitive deficits, and neurological soft signs were present. Hyperactive low achievers had an increased frequency of obstetrical complications. Sex differences were found in predictors of unexpected academic failure. A summary of major findings has been published in a report on the Collaborative Perinatal Project. This study is completed and a monograph is in preparation.

PHS-6040
(Rev. 2-81)

Publications: Broman, S.H. The Collaborative Perinatal Project: An overview. In S.A. Mednick & M. Harway (Eds.): Longitudinal Research in the United States. Boston: Martinus Nijhoff, in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02109-08 DNB

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)
Comprehensive Analysis of the NCPP Data on Congenital Malformations

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	N.C. Myrianthopoulos	Research Geneticist	DNB NINCDS
OTHER:	A.F. Naylor	Research Geneticist	DNB NINCDS

COOPERATING UNITS (if any)
C.S. Chung, Univ. of Hawaii; H. Lubs and M.L. Lubs, Univ. of Miami, Fla.; J. Frias, Univ. of Florida; M. Melnick, Univ. of Southern California, Los Angeles; P. Koslowe, Johns Hopkins Univ., Baltimore.

LAB/BRANCH Developmental Neurology Branch

SECTION
Birth Defects and Genetic Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
6.00	5.00	1.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This is a long-term project to study the epidemiologic characteristics of congenital malformations in singletons and twins; to assess and interpret the influence of maternal, socioeconomic, neonatal, medical and other environmental factors on the occurrence of congenital malformations; to determine the risk of familial occurrence and to elucidate the role of genetic factors and the mode of inheritance of certain malformations; to determine the severity and clinical significance of congenital malformations and their associations with neurological, psychological and sensory handicaps; and to assess the long-range effects of malformations on survival, growth and development.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: This is a long-term project to study the epidemiologic characteristics of congenital malformations in singletons and twins; to assess and interpret the influence of maternal, socioeconomic, neonatal, medical and other environmental factors on the occurrence of congenital malformations; to determine the risk of familial occurrence and to elucidate the role of genetic factors and the mode of inheritance of certain malformations; to determine the severity and clinical significance of congenital malformations and their associations with neurological, psychological and sensory handicaps; and to assess the long-range effects of malformations on survival, growth and development.

Methodology: A congenital malformation is defined as a gross physical or anatomical developmental anomaly which was present at birth or was detected during the first year of life. Malformations have been classified into major and minor categories on the basis of their severity, threat to life and cosmetic significance.

The analysis is divided in 11 parts, and for each appropriate epidemiologic and statistical methods are being employed. In addition, in-depth studies of specific malformations or group of malformations are performed.

Current status and major findings:

I. Epidemiology of congenital malformations in singletons.

This part has been completed. About 15 percent of single-born children had one or more malformations. Half of the malformations were major. Only about a third of malformations observed during the first year of life were diagnosed at birth. Except for three minor malformations which were more frequent among blacks, there were no significant differences in malformation incidences between blacks and whites.

A report of this part has been published.

II. Epidemiology of congenital malformations in twins.

This part has been completed. Twins have significantly more major and minor malformations than singletons but the difference is wholly contributed by monozygotic (MZ) twins. The incidence of malformations in dizygotic (DZ) twins is the same as that in singletons. Monoamniotic twins have more malformations than diamniotic twins. Concordance rates are significantly higher among MZ than among DZ twins for all malformation categories but among specific malformations only those of the musculoskeletal system show significant differences.

A report of this part has been published.

III. A study of the effects of medical, genetic and socioeconomic factors in the occurrence of congenital malformations.

This part has been completed. Multiple birth, pregnancy complications (mostly through hydramnios) and male birth were positively correlated with increased risk in major malformations, whereas maternal weight gain was negatively correlated with major malformations. Maternal diabetes during pregnancy was significantly correlated with single or multiple major malformations.

Over one-third of children of chronic alcoholic mothers show a constellation of developmental deficits and clinical symptoms known as the "fetal alcohol syndrome". An analysis of malformations in children of mothers who took dilantin during pregnancy shows that 11% of these children show a constellation of developmental deficits and clinical symptoms consistent with the "fetal hydantoin syndrome".

Reports of this part have been published.

IV. Special analysis of the effects of diabetes in the mother on the occurrence of congenital malformations in the offspring.

This part has been completed. The risk of having a malformed child in mothers with continuous diabetes is doubled compared to that of non-diabetic mothers, with regard to major malformations and increased significantly with regard to minor malformations. The effect seems to be associated with the severity of the disease and not with the intake of insulin.

A report for this part has been published.

V. A file for genetic studies of congenital malformations.

This part has been completed. A file has been designed to derive empiric risk figures of repeating a malformation when it has once appeared in a family; to identify familial aggregations of specific malformations; and to clarify the mode of inheritance in identified familial aggregations.

The basic file to be used in genetic analyses has been considerably enlarged and has been documented. This "Family Linkage File" contains a record for each NCPP child including all information on its relationships to other NCPP children. It also combines genetic information such as family linkages, twin zygosity, etc., with important maternal and outcome variables such as malformations, minimal brain dysfunction, mental retardation, speech and hearing disorders, seizures, cerebral palsy, and visual disorders.

VI. Study of associations of ABO and Rh blood types with congenital malformations.

This study has been designed to confirm earlier suggestions of association of blood groups with congenital malformations, based on small samples.

The study has been completed. Several associations have been detected, some of which are fortuitous. The most interesting finding is a strong negative association between mother's blood group O and anencephaly. Another strong and interesting association is between pyloric stenosis and Rh incompatibility in boys. The nature of these associations should be explored in in-depth studies.

A report with extensive tabulations has been produced.

VII. Study of the clinical significance of minor malformations.

VIII. Longitudinal study of development, morbidity and survival of children with malformations.

These two parts have been combined for purposes of analysis. The objective of Part VII is to establish which minor malformations are worthwhile detecting and why, and which ones can be ignored or considered as normal variants. Part VIII is a continuation of Part VII and deals with the effects of single and multiple malformations on growth and development.

All cases with multiple malformations have been carefully reviewed. Of 1,477 cases with multiple malformations, 531 were considered to have significant multiple malformations. The remaining 946 were found to have multiple minor anomalies or single malformations. Analysis of 531 cases showed that in 234 (44%) the condition was a localized error in morphogenesis (anomalad); in 154 (29%) a specific syndrome could be identified; and in 143 (26.9%) the pattern of malformation could not be identified.

A special file of multiple malformations incorporating these findings has been produced and the first part of the analysis has been designed. Though lack of computer programming help has slowed down the analysis considerably, this has now been resumed and is progressing satisfactorily.

IX. Study of the effects of maternal factors in the production of congenital malformations.

This part has been completed. Families containing half siblings have been used in the analysis to determine maternal influences, genetic or environmental. Among malformations for which sufficient information was available, clubfoot, congenital heart defects, umbilical and inguinal hernias, polydactyly, and cafe au lait spots occurred with significantly higher frequencies in half siblings than in the NCPP population. The recurrence risks of these malformations were the same in full and half siblings. While this approach cannot differentiate between genetic and environmental maternal factors, it provides clues for formulating and testing biological hypotheses.

A report for this part has been published.

X. Study of 7-year malformations.

This part will study the epidemiologic characteristics of congenital malformations in NCPP children surviving to age 7 years, make comparisons with the 1-year malformations, and provide a basis for studies of the effects of these malformations on neurological outcome, psychological tests performance, and speech, language and hearing performance.

The study is now in progress. The 7-year malformations have been defined, identified, and classified into major and minor. New codes have been assigned for comparison with the 1-year malformations and a new file containing the 1-year and 7-year malformations has been created. Frequency distributions of the 7-year malformations have been produced by race, sex and institution.

Of the original cohort of 53,257 children, 39,640 were examined at 7 years although information about malformations after 1 year is available for 47,115 children. Only 3,844 children were completely lost to study after 1 year. The lost to study children do not have a higher frequency of malformations than the other children at 1 year.

While about 15% of children were found to have major and/or minor malformations through age 1 year, about 19% are found to have malformations through age 7 years. The increase is in eye, upper respiratory tract and mouth, and genitourinary malformations, and tumors. Over 70 new specific diagnoses have been made. Among the most frequent are ocular hypertelorism dental malformation, tumors, malformation syndromes and chromosomal syndromes, some of which were present, but could not be recognized during the first year of life.

A monograph-length report is being written.

XI. Correlation of minor chromosomal variants with congenital malformations.

This part has been carried out as a contract operation with Dr. Herbert Lubs, University of Colorado, Denver, as principal investigator. The study utilizes data which have been developed by five NINCDS Collaborating Perinatal Project institutions which are currently participating in the Denver-based chromosomal study of minor variants.

About 40 "independent" significant associations were found but considering the large number of analyses performed, these are not more than would be expected by chance. The most significant associations were between strawberry/portwine hemangioma and increasing amounts of qh material; and pale Q banding heteromorphisms and skin anomalies. These results indicate that the total amount of qh or p11 and p13 material may be more important in the determination of developmental anomalies than any particular heteromorphism per se.

The study has been completed and an extensive report has been produced.

In-depth studies of congenital malformations

These studies have been planned as a logical extension of the original Program Plan for Comprehensive Analysis of the NCPP Data on Congenital Malformations. The specific objective is to study the epidemiologic and genetic characteristics, and natural history of specific malformations or groups of related malformations.

1. External ear malformations.

This study has been completed. The frequency of external ear malformations was 1.72% in blacks and 0.42% in whites. The frequency of familial cases was 6% in both races. Segregation analysis showed that there was a substantial number of chance isolated cases. In hereditary cases, no distinction could be made between a common recessive trait with 40% penetrance and a rare dominant trait with 20% penetrance, or genetic heterogeneity. A most interesting finding was a significantly increased risk for hearing loss and speech abnormalities among white sporadic cases and a lesser increase among black sporadic cases.

A monograph-length report has been published.

2. Maternal radiation and childhood neoplasia

This study has been completed. The relative risk of childhood malignancies was found to be 2.61 that of controls when mothers were exposed to radiation prior to pregnancy, and 2.59 when mothers were exposed during pregnancy. No significant association with benign neoplasms was detected. High exposures (300 nrads or more of cumulative dose to the gonads) consistently had higher risk than medium exposure (70-300 nrads of cumulative dose to the gonads). The possible effect of preconception radiation on the risk for tumors can be interpreted as supporting the hypothesis that certain tumors are produced as a result of two mutations, either two somatic or one germinal and one somatic.

A report has been published.

3. Neural tube defects

This study attempts to gain insight into the etiology of neural tube defects by comparing the distribution and behavior of a large number of pre- and perinatal factors in patients and controls. The records of 85 patients and over 400 random controls were extensively reviewed. Clinicopathologic correlations have been made which include gross and microscopic neuropathologic findings, measurement and weight of internal organs, and gross and microscopic examination of the placenta. Epidemiologic and genetic analyses have shown that the risk for neural tube defects is related to the length of the interval between conceptions.

A report is being written.

4. Microcephaly

This study will define measurement and clinical microcephaly, and the relation between the two; and investigate those pre- and perinatal variables which may be significant in the occurrence of microcephaly. In a normal group of children correlations between head size and body length were significant, indicating that body length should be taken into account when head size is used as a variable. Norms for head size (corrected for body length) have been derived. An analysis of IQ scores showed that even in normal children head size is positively correlated with IQ. The analysis will be extended to children with IQ below 70, and children with other neurological signs and congenital malformations to determine what combination of factors make up the syndrome of clinical microcephaly. No substantial progress has been made because of lack of computer programming help.

5. Pyloric stenosis

This study will examine possible etiologic mechanisms of pyloric stenosis by comparing the distribution and behavior of pre- and perinatal variables in patients and controls. The records of 105 patients and 210 matched controls have been extensively reviewed. Preliminary analysis continued the association of pyloric stenosis and Rh incompatibility. The NCPP sample is now being augmented by addition of cases ascertained in the Baltimore area.

The study is in progress.

6. Congenital heart defects

This study will attempt to identify genetic and enviromental factors which may be significant in the etiology of congenital heart defects by comparisons of the distribution of a large number of pre- and perinatal variables in patients and controls and by special genetic analysis. Extensive abstracting of records of 392 cases and 784 matched controls has been accomplished and a special file for analysis has been produced. The analysis has been designed and is currently under way. A special genetic segregation analysis has been completed. The results did not suggest major genes as an explanation for the clinical variation; a multifactorial hypothesis, with both genetic and environmental variables acting, seems to fit the data well. No further progress has been made because of lack of computer programming help.

Publications:

Myrianthopoulos, N.C.: The human population data: Critique II. In Melnick, M., Bixler, D. and Shields, E.D. (Eds.): Etiology of Cleft Lip and Cleft Palate. New York, Alan R. Liss, 1980, pp. 357-361.

Shiono, P.H., Chung, C.S. and Myrianthopoulos, N.C.: Preconception radiation, intrauterine diagnostic radiation and childhood neoplasia. J. Nat. Cancer Inst. 65:681-686, 1980.

Clerget-Darpoux, F. and Bonaiti-Pellie, C.: Epistasis: an alternative to the hypothesis of linkage disequilibrium in HLA associated diseases. Ann. Hum. Genet. 44:195-204, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02112-08 DNB

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Neonatal Hyperbilirubinemia

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J. S. Drage	Chief	DNB, NINCDS

COOPERATING UNITS (if any)
P. C. Scheidt, USUHS, Department of Pediatrics
J. B. Hardy, The Johns Hopkins University
E. D. Mellits, The Johns Hopkins University

LAB/BRANCH
Developmental Neurology Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.03	0.01	0.02

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The neonatal hyperbilirubinemia study has been designed to assess the relationship of intermediate levels of serum bilirubin on the subsequent neurological and mental development of NINCDS Collaborative Perinatal Project children. There has been increasing concern that neonatal serum bilirubin levels between 10-20 mg% may be damaging to the central nervous system, not in the classical sense of 'kernicterus' associated with levels above 20 mg%, but rather damaging in more subtle yet clinically significant ways. Neonates have been studied in five birthweight-gestational age categories, by three socioeconomic classes, for a variety of outcome measures, including mental and motor assessment at age 8 months, and a spectrum of neurological findings at age one year which will include motor performance, reflexes, tone, abnormal movements, eye findings and the overall neurological classification of normal, suspect or abnormal. The analysis of Phase I of this study has been published. The analysis of Phases II and III, which include data obtained at ages four and seven years, has been completed. A report on findings is being prepared.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02169 - 07 DNB

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)
Obstetrical Medication and Development in Infancy and Early Childhood

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S. H. Broman	Acting Chief, MRLDS	DNB NINCDS

COOPERATING UNITS (if any)
Dr. Peter Shaughnessy, University of Colorado Medical Center
Dr. Yvonne Brackbill, University of Florida

LAB/BRANCH
Developmental Neurology Branch

SECTION
Mental Retardation and Learning Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.08	.06	.02

CHECK APPROPRIATE BOX(ES)
☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study investigated relationships between obstetric medication and physical and cognitive development through age seven. Subjects were full term infants born to mothers with uncomplicated pregnancies and deliveries. The cohort was drawn from two hospitals in the NCPP. Pharmacological agents evaluated were inhalation anesthetics and six other drugs administered during labor and delivery. Outcomes in the first year of life included items from pediatric and psychomotor assessments. Later outcomes were scores from psychometric examinations, and items from a pediatric neurological examination. Univariate associations between outcomes and drugs were identified, and the significant relationships were examined in multiple logistic regression analyses with other risk factors included. The results suggest that inhalants are associated with deficits in early psychomotor and neuromotor functioning, and that oxytocin is also associated with psychomotor deficit. Scopolamine and secobarbital are related to respiratory difficulties in the newborn, and inhalants, scopolamine, and secobarbital are associated with palpable liver at 4 months. At older ages, scopolamine is associated with slightly lower scores on some cognitive tasks, and oxytocin is associated with lower achievement test scores. A report is in preparation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02171-07 DNB

PERIOD COVERED

October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Compendium of Heritable Disorders of the Nervous System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	N.C. Myrianthopoulos	Research Geneticist	DNB NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Developmental Neurology Branch

SECTION

Birth Defects and Genetic Disorders Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.10	PROFESSIONAL: 0.05	OTHER: 0.05

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose is to prepare a comprehensive list of all known heritable disorders of the nervous system, including disorders and malformation syndromes which, though not primarily neurological, have neurological involvement.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: To prepare a comprehensive list of all known heritable disorders of the nervous system, including disorders and malformation syndromes which, though not primarily neurological, have neurological involvement.

Methods employed: Sources for the compendium are published reports in the past and current literature containing convincing evidence of familial occurrence.

Current status: Recent additions to and deletion from the list have brought the number of neurological disorders to over 900. These have been classified into 23 nosological categories, including malformations, spinal atrophies, ataxias, demyelinating disorders, epilepsies, metabolic disorders, neuromuscular disorders, neoplasms and vascular disorders, mental retardation, syndromes, and others. The list is constantly being revised as new information becomes available.

Publications:

Myrianthopoulos, N.C.: Thirty short articles on neurogenetic disorders. In Vinken, P.J., Bruyn, G.W. and Myrianthopoulos, N.C. (Eds.): Handbook of Clinical Neurology, Vol. 42, Neurogenetic Directory Part I. Amsterdam, North-Holland Publishing Co., 1981. (See Table of Contents for individual articles.)

Vinken, P.J., Bruyn, G.W. and Myrianthopoulos, N.C. (Eds.): Handbook of Clinical Neurology, Vol. 42, Neurogenetic Directory Part I. Amsterdam, North-Holland Publishing Co., 1981, 772 pp.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02234-06 DNB

PERIOD COVERED
October 1, 1980 Through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Febrile seizures study

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K.B. Nelson	Pediatric Neurologist	DNB NINCDS
PI:	J.H. Ellenberg	Mathematical Statistician	OBFS NINCDS
PI:	D.G. Hirtz	Expert Consultant	DNB NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Developmental Neurology Branch

SECTION
Section on Cerebral Palsy and Other Motor Disorders

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.6	PROFESSIONAL: 0.4	OTHER: 0.2

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The NINCDS Collaborative Perinatal Project has provided a large prospectively defined pediatric population, unselected for level of risk, in which to investigate the prevalence and natural history of the most common convulsive disorder of childhood, febrile seizures. A series of papers has delineated the natural history of febrile seizures, identified risk factors for unfavorable outcome, and reviewed the effect of sample selection on outcome. An NIH Consensus Development Conference on Long-term Management of Children with Febrile Seizures was held. Results of the consensus conference have been published in professional and lay journals, and the papers have been edited for a monograph. A major study to evaluate the effects of medications and of recurrent seizures is planned under contract. We have collaborated in designing a study on the EEG as a predictor in febrile seizures, and in a survey on management of febrile seizures.

PHS-6040
(Rev. 2-81)

Project Description: Children in the population of the NINCDS Collaborative Project who experienced febrile seizures were identified, and their seizure histories and subsequent histories examined.

Objectives: To evaluate the prevalence, associated conditions, and prognosis of this extremely common convulsive disorder. Quantification of the risks associated with febrile seizures is necessary for rational decision-making as to therapy.

Methodology: Information abstracted from the records of children with febrile seizures was used to create a tape for data analysis on a time-share system in the Office of Biometry and Epidemiology. Clinical characteristics of children with febrile seizures, and other seizure experience by the age of seven years, as well as results of intelligence testing at seven years, were examined. Sibling controls of children with febrile seizures were evaluated.

Results: Of 1821 children with febrile seizures in the Collaborative Project population, 1706 were followed to the age of seven years. Two per cent had become epileptic by the age of seven, and another one per cent had had at least one afebrile seizure not meeting the definition of epilepsy employed. Race, sex, birthweight and Apgar score were not significant predictors of epilepsy, but clinical features of the seizures, abnormal neurological status prior to the first seizure, and afebrile seizure disorders in the immediate family increase the risk of epilepsy in a child who has had a febrile seizure.

Comparison of 431 children who have had febrile seizures only with their seizure-free siblings indicates that febrile seizures do not "cost" the child a loss in IQ, or an increased vulnerability to early learning disorder. There were no deaths and no acquired motor defects associated with febrile seizures in this series.

Predictors of recurrence, and further refinement of the relationships of characteristics of the child and types of febrile seizures to the risk of subsequent convulsive disorders have been presented. Current activities on this topic include a survey of medical management of febrile seizures in the United States, to establish current practices and whether these differ by geographic area or medical specialty. A consensus meeting on the management of children with febrile seizures was held and an edited monograph on this topic has been sent to press. A study of cognitive and behavioral effects of anticonvulsant medication will evaluate the effects of medications and of recurrent seizures.

Significance: Three to four percent of children experience at least one febrile seizure. This is the most common seizure disorder in any age group, and one of the most common acute problems in child neurology. Considerable disagreement as to optimal medical management exists, and it has been our objective to supply clinically useful information as to the spectrum of risks associated with febrile seizures, as a component in therapeutic decision making.

Honors and Awards: Public Health Service Special Recognition Award to Dr. Nelson, 1977

Public Health Service Special Recognition Award to Dr. Ellenberg, 1978

Public Health Service Special Achievement Award to Dr. Nelson, 1981

Publications:

Nelson, K.B.: Febrile Seizures. In Swaiman, K. and Wright, F. (Eds.): The Practice of Pediatric Neurology, 2nd edition. St. Louis, C.V. Mosby Co., in press.

Nelson, K.B. and Ellenberg, J.H., (Eds.): Febrile Seizures, New York, Raven Press, in press.

Nelson, K.B. and Ellenberg, J.H.: The role of recurrences in determining outcome. In Nelson, K.B. and Ellenberg, J.H., (Eds.): Febrile Seizures, New York, Raven Press, in press.

Nelson, K.B. and Ellenberg, J.H.: Can treatment of febrile seizures prevent subsequent epilepsy?, ibid.

Ellenberg, J.H., and Nelson, K.B.: The efficiency of published recommendations for the treatment of febrile seizures, ibid.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02332-04 DNB

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Analysis of NCPP Twin Data

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	N.C. Myrianthopoulos	Research Geneticist	DNB NINCDS
Other:	F. Clerget	Guest Worker	

COOPERATING UNITS (if any)

NHLBI; M. Melnick, University of Southern California, Los Angeles

LAB/BRANCH
Developmental Neurology Branch

SECTION
Birth Defects and Genetic Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.00	.80	0.20

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This is a secondary area within the program plan for analysis of NCPP data. The objectives of the project are to assess and interpret the influence of maternal, socioeconomic, neonatal, medical and other environmental factors on survival, growth and development, and on abnormal outcome of twins.

PHS-6040
(Rev. 2-81)

Project Description:

Objectives: The objective of the project is to assess and interpret the influence of maternal, socioeconomic, neonatal, medical and other environmental factors on survival, growth and development, and on abnormal outcome of twins.

Methodology: Twins have been classified into monozygotic (MZ) and dizygotic (DZ); and MZ twins into monochorionic (MC) and dichorionic (DC). Comparisons between and among these groups, including singletons, will be made using concordance, correlation and heritability statistics.

Current status and major findings: Studies of the effects of chorion type on normal and abnormal variation showed that chorion type has no effect on and cannot explain the higher frequency of congenital malformations in MZ twins. Likewise, chorion type has no effect on head circumference, height, and right-left asymmetry of dermal ridges. Dichorionic MZ twins have a significantly greater within-pair variation than monochorionic MZ twins for these variables. Chorion type, likewise, had no significant effect on anterior fontanelle development variation in MZ and DZ twins. Anterior fontanelle development is shown to have a significant genetic variance component at four months of age but not at one year, a finding which may be related to the rapid growth witnessed between birth and eight to nine months of age. These data offer little support to prior speculations that monochorial placentas may provide less favorable environment for fetal development.

Currently, the hypothesis is being tested that the higher frequency of congenital malformations in MZ twins than in DZ twins and singletons is due to a 2-hit process which disrupts the developmental genetic clock of the embryo and renders it susceptible to the action of subtle environmental agents. The frequencies of several such variables as drug intake, viral infections, febrile episodes, etc. during pregnancy of mothers of MZ twins are being compared to that of mothers of DZ twins and singletons, for agreement with predictions under the hypothesis.

Publications:

Melnick, M., Myrianthopoulos, N.C. and Christian, J.C.: Estimates of genetic variance for anterior fontanelle development in the NCPP twin population. Acta Genet. Med. Gemellol. 29: 151-155, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 01274-17 DNB

PERIOD COVERED
October 1, 1980 through September 30, 1981

TITLE OF PROJECT (80 characters or less)

Genetic Bases of Neonatal Reflexes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A.F. Naylor	Research Geneticist	DNB NDP NINCDS
OTHER:	N.C. Myrianthopoulos	Research Geneticist	DNB NDP NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Developmental Neurology Branch, Neurological Disorders Program

SECTION
Birth Defects and Genetic Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0	PROFESSIONAL: 0	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project has been discontinued.

PHS-6040
(Rev. 2-81)

TAB 6 -- STROKE & TRAUMA PROGRAM -- STP

ANNUAL REPORT
October 1, 1980 -- September 30, 1981

Stroke and Trauma Program

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

INTRODUCTION - 1-3

CEREBROVASCULAR DISEASE

Prevention, Diagnosis and Therapy - 4-5
Animal Studies of Circulatory and Metabolic Factors - - - - - - - - - - 6
Comprehensive Stroke Center Program - - - - - - - - - - - - - - - - - - - 7
Cerebrovascular Survey Report - 7
Meetings - 7

POSITRON EMISSION TOMOGRAPHY - 8-13

SPINAL CORD INJURY - 13-18

HEAD INJURY - 19-20

CNS NEOPLASMS - 20-21

NEURAL REGENERATION AND PLASTICITY - - - - - - - - - - - - - - - - - - - 21-24

PAIN - 24-25

CONTRACT NARRATIVES

Comprehensive Stroke Centers - 26-27
N01-NS-8-2385 University of Rochester
N01-NS-8-2386 North Carolina Heart Association
N01-NS-8-2387 University of Oregon Health Science Center

Comprehensive Central Nervous System Trauma Centers - - - - - - - - - - 28-29
N01-NS-9-2312 University of California, San Diego
N01-NS-9-2313 Albert Einstein College of Medicine
N01-NS-9-2314 University of Texas Medical Branch

ANNUAL REPORT
October 1, 1980 -- September 30, 1981

Stroke and Trauma Program
National Institute of Neurological and Communicative Disorders and Stroke

INTRODUCTION

The Stroke and Trauma Program of the NINCDS is responsible for basic and applied research and related training relevant to cerebrovascular disorders, the effects of head and spinal cord injury, neural regeneration and plasticity, brain tumors, chronic pain and other related research. It also serves as the institutional focal point for research on positron emission tomography (PET), psychosurgery and manipulative therapy.

The Stroke and Trauma Program covers those areas and neurologic disease entities which are of the highest incidence and prevalence, cause the severest morbidity and mortality, take the largest toll in life and cause the greatest aggregate amount of suffering. Included are the vast number of head, spinal cord and peripheral nerve injuries, the considerable number of strokes and their sequelae which are becoming more apparent in an aging population, the problems of preservation and regeneration of neuronal function following these diseases, brain tumor (the second leading cause of pediatric death) and chronic pain resulting in distress and extensive loss of productivity. High priority therefore is given to applied and clinical investigations with direct relevance to the pathogenesis, diagnosis and treatment of these diseases. Prevention of such diseases is the ultimate intent. However, in order to prevent these disease one must first understand them and their sequelae. The Program contains discrete as well as overlapping components of basic, applied and clinical reseach and utilizes the several administrative instruments of program support (i.e., research project grants, program project grants, clinical research center grants, cooperative clinical trials, resource contracts, and service contracts).

The number of applications for research of program relevance has decreased by 6% compared to FY'79. The allocation of funding was therefore:

Stroke	35%
Trauma	28%
Regeneration	19%
Neoplasms	03%
PET	14%
Other	02%

Of the 207 grant applications received during FY 1980, 61% were approved by Study Section. Of those, some 62% were approved by Council and awarded. Therefore, of all grant applications received by STP during this year, 38% were approved and awarded. Not only has there been a 6% decrease in the number of grant applications received, but the percentage of those approved and awarded has slipped from 42% to 38%.

The Cerebrovascular Clinical Research Centers (CCRC) funding major university and medical centers throughout the country make up a significant segment of the stroke program. A new center at the University of Oregon has been added. Currently there are 12 centers serving as the focal point in research on etiology, natural history, diagnosis, treatment and pathophysiologic events related to cerebrovascular disease. These research programs are broad, multidisciplinary and only interrelated in a general sense. Studies carried out by the CCRC include determining those factors which contribute to irreversible brain damage caused by ischemia and hypoxia utilizing experimental models of stroke and shock. New investigative tools or refinements of existing approaches are examining regional blood flow, regional glucose metabolism, mitochondrial function, ion flux, tissue metabolites, cortical redox states and ultrastructural changes. Clinical studies are directed first at intensive care and studying of stroke patients, assessment of their regional cerebral blood flow and the specific effects of medical and surgical therapy. Although the CCRC Program has been in effect for more than a decade, there has been only informal coordination and cooperation among the various centers. In the future, it is hoped that by using the Comprehensive Stroke Center Research Program as a model method of focused clinical research and the potential of cooperative agreements, improvement in the coordination and cooperation between CCRC Programs can be obtained.

The Comprehensive Stroke Center Program is completing its second phase. The first phase, consisted of pilot and feasibility studies of one year's duration, and indicated that more complex studies on stroke patients could be carried out with appropriate data generated. The second phase has involved the development of baseline patient data information which attempts to demonstrate that the transfer of currently employed therapeutic modalities into the community does in fact have an effect on outcome, morbidity and mortality of the stroke patient. In addition these three centers have evolved a common data format which will allow intercomparisons between them.

The grant funded Head Injury Clinical Research Centers remain at the forefront of brain injury research. More highly targeted are the efforts of the Comprehensive CNS Trauma Centers, who are involved in broad epidemiologic and therapeutic studies (partly in conjunction with the Coma Data Bank of the Office of Biomety and Field Studies, NINCDS) and community organization, education, and outreach programs. Coordination and cooperation among trauma center participants have been excellent.

Spinal cord injury research contains two major thrusts; 1) to examine the secondary and cascading reaction of the spinal cord to injury which results in increased deficit and 2) to assess the effectiveness of currently available methods of diagnosis and treatment and in doing so develop significant data on a large cohort of patients. To that end, a significant portion of spinal cord injury research is being carried out at the five Spinal Cord Injury Clinical Research Centers and through the coordinated efforts of the Yale Spinal Cord Injury Clinical Research Center registry. Prevention of spinal cord injury must occur prior to the event, but in those cases where injury does occur prevention of the secondary effects and thus avoiding more severe disability is of extreme importance.

Considerable emphasis is being placed upon the development and fostering of basic research in nervous system regeneration and plasticity which is vital for improvement into the treatment of this disease. Regeneration of nervous tissue is a global issue which pertains to the brain, spinal cord and peripheral nerves. Much of what can be learned from one area is directly relevant to others as many physiologic arameters are shared (example, the blood brain barrier). While the basic properties of regeneration and plasticity must be unraveled in the laboratory setting, the clinical events surrounding spinal cord injury and its subsequent effects can be studied through the activities of the Comprehensive CNS Trauma Centers as well as the Spinal Cord Injury Clinical Research Centers. As a better understanding of these patients evolves, appropriate stratification factors and prognostic indicators can be developed which will aid in the design of eventual clinical trials.

Positron Emission Tomography (PET) is a high visibility targeted program of the Institute. Fourteen percent of the STP effort goes toward the development of this complex methodology capable of unraveling the real time biochemical events of the brain. During the past year the instrumentation in most centers has been rapidly developing to the point where it will be on-line for full experimental purposes. The production of isotopes with labels in a variety of places has allowed investigators to demonstrate normal brain function at work and at rest as well as abnormal brain function secondary to stroke, epilepsy or tumor. The prevention of these diseases and their sequelae may well be obtainable once we understand the basic cellular and subcellular metobolic events which differentiate them from normal tissues.

Clinical investigators trained in the disciplines of basic science remain in short supply. The lure of private medical practice compared to the frustrations of demanding research are difficult to overcome. Nevertheless it is this cadre of young, trained, critical investigators who will become the research leaders of the future. Thus emphasis must be given to the recruitment and development of scientifically trained clinicians through the use of institutional fellowship and teacher-investigator award mechanisms.

The NINCDS Stroke and Trauma Program utilizing the funds and other resources made available to it has served as the institutional focal point for the planning and operation of research indeavors in cerebrovascular disease, brain and spinal cord trauma, brain tumors, regeneration and other related research. Such efforts are directed toward understanding the basic disease process with the expectation of eventually preventing or ameliorating these diseases and their sequelae. The limit of resources available now and in the future require a continuing reevaluation of program goals and objectives to make the most effective use of the funds which are available. It is the program's intent to obtain the best possible research in all areas of endeavor so as to improve the quality of care of patients with these diseases and eventually prevent them.

I. CEREBROVASCULAR DISEASE

A. Prevention, Diagnosis and Therapy

A group of bioengineering investigators at Bowman Gray School of Medicine form an important national resource in ultrasonic imaging. While much current emphasis has been placed on evaluating the extracranial carotid system, noninvasive techiques for similar evaluation of the intracranial vasculature are now available. Studies on the intracranial arteries have been limited to invasive techniques such as arteriography, by the relatively elaborate equipment needed, or time duration of the study, or by the administration of agents, such as xenon or radioactive ammonia. In addition, these diagnostic tests are performed on patients who have severe symptoms and disease, either as a precursor or as a result of stroke, and usually can not be repeated during the same hospital visit. The same analysis techniques used for the extracranial carotid arteries can now be applied to early detection of intracranial atherosclerosis and the effects of therapeutic regimens followed. The dynamics and changes in dynamics of the major intracranial arteries can be followed on-line at the patient's bedside, or in other patient environments, as a function of time with or without additional therapeutic or test measures.

Within the past year the Stroke Center at Cornell University Medical College has acquired a real-time B-mode ultrasonography unit designed for the investigation of cervical carotid bruits. It is coupled with a doppler system to assess flow as well as anatomy. Over 20,000 New York City employees who undergo regular health examinations have been screened, and hypertension has been detected in approximately 2,000 of them. Asymptomatic carotid bruits have, in turn, been identified in about 5% of this hypertensive population. A comparable group of age-matched nonhypertensive individuals with carotid bruits have also been identified. These groups of patients will be compared with each other and to a group of normal controls without carotid bruits in terms of their development of cerebrovascular disease and in terms of the presence of carotid pathology detected with ultrasound.

Investigators at Washington University, St. Louis, have developed a method of labeling platelets with Indium III for use as a noninvasive test for detecting and quantitating the accumulation of platelets at sites of arterial injury. Tests used in the past have produced only indirect evidence concerning the magnitude of platelet-blood vessel interactions throughout the entire body. In contrast this technique now being used permits evaluation of platelet deposition on individualized vascular lesions in patients.

The primary objective of a collaborative study of extracranial/intracranial anastomosis is to determine whether EC/IC arterial anastomosis will reduce, by 50% or more, the incidence of first or recurrent complete strokes in patients with certain forms of cerebrovascular disease. The first patient was entered into the study in September 1977. The total patient accrual as of May 1981 was over 1,000 patients from over sixty centers in North America, Europe and Japan. Quality control continues to be excellent. The Japanese have a striking preponderance of middle cerebral artery cases contrasted with the preponderance of internal carotid artery cases entered from North America and Europe, thus adding an important intercomparative factor. Furthermore, their incidence at entry of the important risk factors of diabetes, history of myocardial infarction, angina and intermittent claudication is strikingly lower than in the other racial groups. Therefore, this important group will be treated in the initial analysis as separate from the others, and sample-size calculations are being maintained as the goal for the North American and European entries with the Japanese as a parallel study. A major problem emerging is that the distribution of patients into each of six diagnostic categories is different than that which has been anticipated and, therefore, accrual of patients will continue for an additional year.

Despite advances in medical and surgical care of ruptured aneurysms over the last 30 years, the mortality and morbidity of subarachnoid hemorrhage (SAH) remain high. Medical therapy with antifibrinolytic drugs is effective in reducing preoperative rebleeding, and safe effective surgery is available. Yet, overall results of treatment demonstrate that patients continue to die or become disabled at unacceptable rates as a consequence of complications related to the initial hemorrhage, such as vasospasm or subseqent rebleeding. Therapeutic advances must be aimed at patients hospitalized within a few days of SAH. One promising approach under investigation is the value of early intracranial operation, but its superiority over delayed intracranial operation must still be proven. A collaborative study has recently begun at The University of Iowa with the objective of decreasing the morbidity and mortality from ruptured intracranial aneurysms by determining the optimal time for surgical obliteration of the aneurysm. Patient acquisition into this study began in December 1980. As of May 1981, 422 cases had been registered and data on 200 patients received from 63 of 67 centers in North America and Europe. The investigators indicate that they plan to collect the information on 2000-2700 cases over a period of 36 months. Among this number, it is anticipated that at least 400 will have been operated on 0-72 hours after subarachnoid hemorrhage and it is in this group that the critical judgment is to be made as to whether patients with SAH would have less overall morbidity and mortality if operated on earlier than is the common current practice.

At the present time, no effective or agreed upon form of medical therapy exists for thrombotic strokes. From the known mechanisms of thrombotic strokes and the lessons gained from the cardiological experiences with angina and myocardial infarction, it is clear that acute stroke therapy must advance to a more molecular level. A new Stroke Clinical Research Center at the University of Oregon Health Sciences Center is beginning a pilot study of the effects of prostacyclin infusion in patients with acute cerebral ischemia. The rationale for the use of prostacyclin in strokes is based upon its action as a vasodilator and as an inhibitor of platelet aggregation. The mechanism of action of prostacyclin in inhibiting platelet aggregation is attributed to its ability to increase platelet cyclicAMP through activation of adenyl cyclase.

The evaluation of two treatment protocols, namely vasopressor therapy for normotensive patients with acute strokes and hyperbaric oxygen therapy for hypertensive patients with acute strokes has been initiated at the University of Pennsylvania. These two studies have been linked by a common methodology for case finding, entry into study and allocation to either of the two protocols for random assignment to treatment and control groups. The purpose of each study is to evaluate the immediate and sustained efficacy of the intervention on cerebral blood flow and functional performance of stroke patients. Both studies require repeated measures using standardized and reliable data collection devices.

B. Animal Studies of Circulatory and Metabolic Factors

There is substantial evidence for the existence of dense noradrenergic innervation of cerebral blood vessels and considerable progress is being made in our understanding of the various physiological and biochemical defects that are caused by cerebral norepinephrine depletion.

The long-range goal of a research project at the University of Miami is to study the role of cerebral norepinephrine in the control of local cerebral circulation and tissue perfusion as well as to define this role and the reaction of brain tissues to insults of hypoxia and ischemia. One of the main objectives is to determine the effects of a variety of pharmacologic agents, that mediate their effects via noradrenergic mechanisms, on cerebral perfusion and metabolism so as to modify these functions during pathophysiological conditions such as stroke. Data obtained demonstrate that lesions of the locus ceruleus in rats and the resultant depletion of norepinephrine influences oxidative metabolism in situ. This influence was not observed under conditions of low energy demand during a resting state but was seen during increased metabolic demand induced by direct cortical stimulation. These results are consistent with a role for norepinephrine in the regulation of cerebral oxidative metabolism in response to sudden increases in energy requirements.

In a related study conducted at the Massachusetts General Hospital, investigators have for the first time been able to define biochemically the pharmacological characteristics of the cerebral vasculature adrenergic receptor. This finding has implications for the design of pharmacological agents with which to alter cerebral blood flow and vascular permeability. For example, on the basis of these and previous results, one could predict that potent, lipophilic, $beta_2$ agonists given systemically should be able to increase cerebral blood flow without causing concomitant tachycardia and systolic hypertension. Such agents would have potential use, for instance, in conditions of decreased cerebral perfusion that can occur following an aneurysmal bleed.

Neuronal rearrangements appear to be an important mechanism for recovery of function after stroke or head injury. Investigators at Duke University have characterized an unusual neuronal rearrangement in the rat hippocampal formation in which peripheral sympathetic nerves apparently replace damaged central cholinergic neurons. The new fibers are clearly peripheral since they disappear after superior cervical ganglionectomy. Sympathetic nerves appear two to four weeks after lesions damaging the medial septal nucleus, but not when other known hippocampus afferents (even locus ceruleus fibers) are lesioned. The topography of the new sympathetic fibers matches well the normal distribution of septohippocampal fibers in the hippocampus. Furthermore, partial lesions of the medial septum resulting in partial loss of cholinergic neurons in the hippocampus elicit the appearance of sympathetic fibers only where cholinergic neurons have been lost. This neuronal rearrangement is particularly well suited for experimental studies since: (1) the neurotransmitters have been identified; (2) the new neurons arise from an easily accessible peripheral ganglion with a relatively straightforward function; and (3) this rearrangement takes place in adult brain. While some features of the arrangement are unique, its study will probably be useful in understanding the biological basis of recovery of function after stroke.

C. Comprehensive Stroke Center Program

The Comprehensive Stroke Center Program is completing its second phase. The first phase consisted of pilot and feasibility studies of a one year duration which indicated that epidemiological/clinical studies on stroke patients could be carried out. The second phase involves the development of baseline patient data information, which attempts to demonstrate that the transfer of currently employed therapeutic modalities into the community does have an effect on outcome, morbidity and mortality of the stroke patient and that uniform data and observation techniques can be utilized. The members of the Comprehensive Stroke Center Program have met six times during the past year and have established a commonality of purpose and attack. A large amount of comparable data from geographically distinct areas, such as the northwest (Oregon), northeast (Monroe County, NY) and the midsoutheast (North Carolina) is in the developmental stages and will be authenticated and become available during this year. The completion of this work and the publication of its results is expected during the next year.

D. Cerebrovascular Survey Report

A fifth edition of the Cerebrovascular Research Status Report has been published. The purpose of this report is to provide reviews of the current status of various aspects of cerebrovascular disease and to provide an extensive list of bibliographic citations. The reviews by authors in selected fields are valuable to individuals working in the general area and to those interested in obtaining current information. This new edition places increased emphasis on computerized tomography scans and reconstruction of arteries, physical therapy and rehabilitation.

E. Meetings

The agenda of the Cerebrovascular Clinical Research Center Workshop held in February 1981, reflects the areas in cerebrovascular research which are currently receiving the greatest attention. The following topics were discussed: the Central Noradrenergic System in Cerebral Vascular Disease; Monitoring and Cerebral Ischemia; Clinical Application of Cerebral Blood Flow Measurements; Non-Invasive Extracranial Techniques for Cerebral Vascular Disease; Prostaglandins and Cerebral Vascular Disease; Positron ECT Scanning and Cerebrovascular Disease.

Another meeting of interest was a satellite symposium on neural control of cerebral blood flow supported by NINCDS which was held prior to the Tenth International Cerebral Blood Flow meeting in July 1981. The program included: the role of sympathetic nerves on CBF, effects of neurotransmitters, the physiological role of cholinergic innervation, the role of brain stem regions in regulation of CBF (possibly through intrinsic mechanism), and neural regulation of vascular permeability and filtration. Information is rapidly accumulating in this field and this symposium should go a long way toward focusing on important areas and separating fact from opinion.

II. POSITRON EMISSION TOMOGRAPHY

An orientation meeting of the Program Directors of each of the major PET programs was held in December 1980. The directors discussed the research underway or planned, progress in establishing the major facilities - scanner and cyclotron - and the key personnel involved in their programs. This meeting provided worthwhile information with a good overview of the research activities. Another such meeting will be held in the near future as these programs start the third year.

During the past year the NeuroECAT tomograph has been completed and has become the principal scanning instrument at UCLA. Tomographic images of brain metabolism in post-stroke aphasics using ^{18} F-deoxy-2-fluro-D-glucose (FDG) positron emission computed tomography (FDG PET) showed areas of metabolic depression extending beyond the zones of infarction determined by x-ray CT. To evaluate the relationship between language abnormalities and anatomic or metabolic lesions, right-handed aphasic patients had FDG PECT, x-ray CT, and the Boston Diagnostic Aphasia Examination (BDAE). Local cerebral metabolic rates for glucose (LCMRglc) were determined for thirteen brain areas in the damaged hemisphere and were compared to the opposite hemisphere. Corresponding areas on x-ray CT scans were graded by a neuroradiologist on a five point scale for severity of damage. The BDAE subtests were reduced to eleven mean scores, and were compared to either metabolic or CT data using correlational analysis.

The findings suggest that language correlations with structural damage may be deceptive if abnormal function in remaining cerebrum is ignored. The correlations from metabolic rates, suggest that areas posterior, inferior, and superior to the traditional Wernicke's area may be important in the abnormal language of these aphasics.

Over 100 ictal and interictal PET scans using FDG in epileptic patients have now been performed at UCLA and characteristic patterns of local cerebral metabolic rate for glucose (LCMRglc) have been observed in a variety of epileptic conditions. PET and EEG provide information regarding alterations in local cerebral function associated with epilepsy that appear to be complementary, rather than redundant. Ictal PET scans demonstrate zones of increased $\mathrm{LCMR}_{\mathrm{glc}}$ that correspond to seizure spread, as well as seizure origin, but are not reliable for localization of epileptic focus. There is good agreement, however, between the location of a zone of decreased $\mathrm{LCMR}_{\mathrm{glc}}$ observed on interictal PECT scans and the site of ictal onset determined by depth electrode EEG telemetry. When surgery has been performed to remove an EEG identified epileptic focus, in the absence of a radiologically demonstrated structural deficit, there is a high correlation between the location and degree of the interictal PET identified hypometabolic zone and the location and severity of pathological changes observed microscopically in the resected specimen. At the present time PET scans are performed routinely at UCLA on all patients with intractable partial seizures evaluated for surgical therapy. Although a hypometabolic zone alone is not sufficient to identify a potential lesion as epileptogenic, this information, coupled with surface EEG data can, in many patients, accurately identify the epileptic focus and obviate the need for invasive depth electrode EEG recordings. A PET defined zone of decreased $\mathrm{LCMR}_{\mathrm{glc}}$ now constitutes one of the major criteria utilized at UCLA for decisions regarding depth electrode implantation and surgical therapy for epilepsy.

Local cerebral metabolism was studied in Huntington's disease patients ranging in age from 17-71 years who had disease durations from 1-15 years. Local cerebral glucose utilization for major grey and white matter structures was determined. The extent of caudate, central and cortical atrophy was determined and the results compared to those with age-matched controls. Not all patients had caudate atrophy; when present, striatal atrophy was greater in those with longer disease durations. But almost all patients had profound striatal hypometabolism, and three patients with early disease had little or no evidence of striatal atrophy.

Determination of cerebral glucose metabolism (CMRglc) in younger patients with a clinical diagnosis of Alzheimer's Disease revealed an almost linear correlation between the degree of dementia and the decrease in glucose metabolism. In older patients with a diagnosis of senile dementia of the Alzheimer type, on the other hand, the decrease in metabolic activity was not as consistent with the degree of dementia but patients in both groups showed decreased CMRglc when compared to age-matched, non-demented control subjects. Thalamic metabolic activity was relatively decreased in both age groups but never as great nor as directly related to the degree of dementia. Individual patients showed different cortical areas (e.g., frontal, parietal) with maximum metabolic decrease but data was insufficient to link these focal changes with specific symptomatology. Studies of selected patients with dementia from other recognized causes (Huntington's Disease, Wilson's Disease, normal pressure hydrocephalus, multi-infarct dementia, Jakob-Creutzfeldt Disease) revealed considerably less or no decrease in CMRglc in comparison to normal subjects. A patient with Pick's Disease, however, showed marked reduction in CMRglc.

At Brookhaven National Laboratory construction of PET VI is virtually complete and testing is in progress. The PET III is being used as a back-up instrument but it is expected that all human and animal studies will be transferred to PET VI before the end of this calendar year. The Division of Energy and Environment has decided to provide funds for a cyclotron solely dedicated to the PET program with delivery scheduled for January 1982. In the meantime the Brookhaven National Laboratory 60" cyclotron is being used for current studies. The focus on ^{18} F-fluorodeoxyglucose (FDG) remains the cornerstone of the radiopharmaceutic program. Demands from the program project and outside users require a continuing effort in upgrading target systems and improving the synthetic procedure. Introduction of a new step has improved the purity of the ^{18}F-FDG.

The research involving human subjects has been especially rewarding in the Senile Dementia and Schizophrenia projects. Substantial progress has been made in the Senile Dementia work in correlating pathology noted on CT scans with metabolic rates measured by the PET technique. Future work will attempt to correlate specific tasks with metabolic rate and the relation of drug intervention to metabolic rate. There is promise that PET-^{18}FDG studies may be useful in the future in diagnosis and in following the results of therapy. In the Schizophrenia project the hypothesis of hypofrontality continues to hold, especially when correlated with internal structures in the same individual and in relation to normal individuals. PET VI will make a very appreciable difference in these studies. In anticipation of possible clinical studies, a number of preclinical studies have been initiated to elucidate the effects of nigro-striatal DA degeneration on cerebral glucose metabolism. The effects of monoaminergic neuronal systems on glucose utilization in animal models which mimic Parkinson's disease are now being investigated. In particular, the following studies are in progress:

Monkeys with unilateral lesions in the ventromedial areas of the brain stem exhibit neurological and neurochemical deficits which are similar to those observed in Parkinson's syndrome. Thus, monkeys with Ventromedial Thalamus lesions were found to be useful models for studies of the role of monoamines in extrapyramidal dysfunctions. Furthermore, with the development of the (C^{14})-2-deoxyglucose (2-DG) autoradiographic method of Sokoloff, it became possible to measure the rate of glucose utilization in specific regions of the brain. More recently, ^{3}H-2-DG was employed for measuring glucose utilization in specific areas of the brain (2,3,). This procedure estimates 2-DG in specific regions of the brain following intravenous and intraperitoneal injection of the isotope. It is also possible to separate unreacted 2-DG from 2-deoxyglucose-6-phosphate (2-DGP) by ion exchange chromatography.

These methods are now being tested for estimation of glucose utilization in specific regions of the brain in monkeys with VMT lesions. These studies will determine (a) whether degeneration of nigro-striatal DA pathways results in an alteration of the glucose utilization in specific regions of the monkey brain; (b) whether DA agonists affect the utilization of glucose metabolism to the same extent of the lesion side as on the intact side.

It is planned to study regional cerebral glucose metabolism in patients with Parkinson's disease. The regional glucose metabolism and the regional cerebral blood flow in the caudate putamen capsule region and in the frontal-parietal cortex will be evaluated with the PET technique. Studies will be performed with the patient at rest and during a well defined motor activity. The same patients will then be studied following treatment with anti-Parkinsonian agents which are known to stimulate specific dopamine (DA) receptors. Since the Parkinsonian patients, in addition to Sinemet, are now being treated with bromocriptine which stimulates DA receptors not linked to adenylate cylase, and with pergolide which stimulates DA receptors linked to the adenylate cyclase, studies are planned to study the effects of these two drugs on glucose utilization in the brain. Fifteen patients will be evaluated including at least five patients who have never been treated with levodopa and ten who are under treatment with levodopa, but in whom levodopa is to be discontinued as part of their treatment (levodopa drug holiday). In addition, five patients who are treated with levodopa and bromocriptine, and five others who are treated with levodopa and pergolide will be studied.

Progress in management of stroke has been largely in diagnosis, based on systematic correlations of clinical findings with post-mortem and radiographic demonstrations of pathologic changes. Over the past 30 years elegant clinico-pathological studies have led, for example, to descriptions of the clinical syndromes of carotid occlusive disease, lacunar disease and cerebellar hemorrhage. However, advances in the treatment of stroke have been limited by a lack of sensitive methods for monitoring pathophysiologic changes in brain. By correlating acute changes in cerebal blood flow (CBF) and metabolism with clinical course, one might identify physiological patterns that characterize viable tissue and then explore therapy that alters impaired tissue function to improve clinical outcome. Such clinico-physiological correlations would be as important for designing rational treatment for stroke as clinico-pathologic correlations have been in facilitating diagnosis.

At the Massachusetts General Hospital, positron imaging techniques are being used for in vivo physiological studies in stroke patients. These studies suggest that positron imaging can identify acute physiological changes that relate to tissue viability and outcome. On the basis of the initial results, it appears justified to attempt to use the positron data to stage the severity of a stroke lesion. Stage one would be an ischemic lesion with intact or minimal impairment of metabolism; stage two, metabolically injured but viable tissue; stage three, infarcted and therefore nonviable tissue. Qualitative studies have identified changes which are consistent with these three stages. Using quantitative results, one should be able to determine whether it is possible to define precise thresholds and ranges of CBF and metabolism for each stage. If one can identify values for CBF and metabolism (at rest or in response to a physiological challenge) that characterize the severity of the lesion and tissue viability, one can apply more rational therapy.

At Johns Hopkins University the program for the study of "Neuroreceptor Binding in Man" is directed toward the *in vivo* localization and quantification of dopamine and opiate receptors in animals, normal human beings, and patients with selected neurological and psychiatric diseases utilizing C-11 and F-18 labeled receptor binding radiotracers. During the past year efforts have been directed towards five specific areas. These are: (a) continued preparation of the necessary facilities, (b) synthesis of required non-radioactive precursors and analogs of benperidol, spiperone and pimozide, (c) investigation of methods for preparing and purifying appropriate radiolabeled compounds, (d) *in vitro* screening of new compounds designed to bind selectively with high affinity to dopamine receptors, and (e) correlation between *in vitro* and *in vivo* binding of opiates.

A detailed study of the regional pharmacokinetics of several tritiated opiate agonists and antagonists in the mouse brain has been completed. The object of this study was to determine the properties of a compound which enable it to be used for *in vivo* localization of opiate receptors in brain. By doing this it may be possible to predict what compound should prove ideal for *in vivo* receptor localization without the necessity of studying it *in vivo* and also to gain a more fundamental understanding of receptor-ligand interactions *in vivo*.

Significant progress has been made at the University of Miami in studies of cerebral metabolism. Correlations between brain enzyme activity and ammonia uptake now make it possible to better understand the factors regulating ammonia uptake by the brain. This is most important in patients with cirrhosis of the liver, where hyperammonemia produces coma. Preliminary studies have also shown that the blood-brain barrier becomes more permeable to ammonia in animals with chronic portacaval shunts, perhaps explaining experimental and clinical observations of increased cerebral sensitivity to neurotoxins in patients with liver disease. Finally, preliminary studies, required to test model assumptions, are leading to the development of a strategy to measure ^{11}C-glucose metabolism in the brain and perhaps overcome problems associated with required assumptions when glucose analogs are used.

Iodoantipyrine (IAP) labeled with carbon 11 has been shown to be a suitable tracer for measuring local cerebral blood flow in man. Carbon 11 IAP was injected as a bolus into the carotid artery of anaesthetized rats and its cranial clearance monitored by collimated probes in a coincidence circuit. The cerebral blood flow values using this method were in excellent agreement with those obtained using the commercially available carbon 14 labeled IAP. Results of this validation were presented at the Tenth International Symposium in Cerebral Blood Flow and Metabolism.

Whole brain ^{11}C-valproate content has been monitored as a function of time after an i.v. bolus of the label in order to measure rate constants for transfer of the drug to the brain. These studies are being extended to monkeys and are an essential first step in eventual human studies. Monkeys are being given intracortical injections of blood to produce a chronic seizure focus, to be studied during development. This is the first practical model of post-traumatic seizures and promises to yield valuable information for this important cause of epilepsy.

Muscarinic receptors have been studied with sub-saturating doses of Quinuclidinyl Benzilate (QNB) with the hope that this highly specific ligand would be a useful agent for PET studies. Animal studies have shown that sub-saturating doses do not distribute according to the known pattern of QNB receptors in the brain. Saturating doses are too hazardous for man, and attention has been directed toward studies of ^{11}c-scopolamine. This safer agent can be given in higher doses, exceeding the number of free receptors. Under these conditions the ligand distribution should reflect receptor distribution.

At the University of Pennsylvania considerable effort has been expended on software development for the PET V. In an effort to improve image quality, the various programs have been examined in detail and rewritten. There has been a noticeable improvement in the visual quality of the reconstructed images. These new programs have also considerably reduced the processing time. Previously, 40 minutes were required to process the 7 slices with corrections for attenuation. With the new software this now takes only 13 minutes.

The critical organ in fluorodeoxyglucose studies is the bladder. In order to provide an accurate estimate of the radiation dose to the bladder in man, the bladder-time course of uptake was measured in a series of 10 subjects undergoing fluorodeoxyglucose studies with the PET III at Brookhaven National Laboratory. The mean bladder dose was found to be 435 mrads/mCi. The usual dose of fluorodeoxyglucose is 5 mCi; therefore, the bladder wall receives a dose of approximately 2.2 rads, which is well within the permitted dose of 5 rads to the critical organ.

In the past year investigators have completed preliminary visual studies. Ten subjects were stimulated with a high contrast, black and white, patterned, visual stimulus to the right (N = 6) or left (N = 4) visual hemifield. Six blindfolded subjects served as controls. They have been able to consistently demonstrate that visual stimulation restricted to one visual hemifield results in an increase in glucose metabolism in the contralateral occipital cortex.

A series of six young normal male volunteers and four elderly normal control subjects were studied along with six patients with dementia. The metabolic rate for glucose for various areas of the brain were determined in all three groups. In the young normal controls the metabolic activity was distributed symmetrically in both hemispheres with an average value of 6.6 mg/100 gm/min in gray matter. In the elderly controls and the patients with dementia the pattern of metabolic activity was distinctly different from the young control subjects. There was a significant right to left ratio difference in metabolic activity ranging from 26% to 60% higher on the right. In addition the mean value for grey matter glucose consumption was significntly different in these older subjects compared to the young controls. The value for the elderly controls was 2.7 mg/100 g/min and for the patients with dementia 2.4 mg/100 g/min, an insignificant difference.

Auditory studies involved the presentation of non-meaningful connected discourse (a story in Hungarian) to subjects unfamiliar with this foreign language. This allowed comparison of cortical metabolic activity resulting from auditory stimulation with both meaningful (a factual story in English previously completed) and non-meaningful linguistic connected discourse under conditions of a sustained attention task. Seven normal hearing young adults served as the subjects of this study and eight normal hearing young adults served as controls. All seven subjects who received the auditory stimulus exhibited substantially greater right hemisphere temporal lobe metabolic activity which was significantly different from the non-stimulated control group. This unexpected result may be explained by the fact that this was a sustained attention task and that the attentional factor was taxed more than language reception in the performance of the experimental task.

A study has been initiated to examine the effect of verbal and spatial tasks on glucose utilization in the temporal regions of the two cerebral hemispheres. Four subjects have been studied during a verbal analogies task and three during a spatial line orientation task. These data are still in the process of being analyzed but preliminary results seem to indicate that there is an increase in glucose consumption in the left hemisphere during the verbal task and in the right during the spatial task in these right-handed subjects.

In the future, stroke patients with somato-motor deficits will be studied to provide information based on local decreases in cerebral glucose metabolism. Further, these patients will be scanned to assess the recovery of function. The metabolic data will be correlated with the CT scan and neurological data.

III. SPINAL CORD INJURY

Spinal cord injury remains an extremely costly biomedical problem. As a result of automobile accidents, war-related injuries and sporting accidents, an unacceptable number of young adults, young men in particular, are relegated to limited and dependent futures.

The five Spinal Cord Injury Research Centers supported by the NINCDS continue to be principal contributors to fundamental and clinical research in the area of central nervous system (CNS) trauma. The centers are located at New York University, Yale University, Ohio State University, The Medical University of South Carolina and The University of Texas at San Antonio. While a common goal binds the several centers, and while some research themes are common to several, each has developed unique interests which serve to give the broadest coverage to the problems associated with spinal cord injury and regeneration.

The Yale group is diversified in interest, approach and expertise. Recent circulatory studies using the hydrogen clearance and antipyrine methods provide support for previous findings that the major effect of severe spinal cord contusion is reduced blood flow. The sequence of changes that occur in spinal cord blood flow (SCBF) after trauma do not appear to be dictated simply by blood pressure. Although the blood pressure falls within minutes after trauma, blood flow within or above the normal range is maintained for approximately one hour. Second, blood flow at some sites may recover to mean control levels in cats in which the blood pressure remains depressed. The findings illustrate some of the advantages and disadvantages of each of the two techniques of SCBF measurement. The hydrogen electrode technique permits measurement of control SCBF prior to trauma and serial post-traumatic flows. Thus, one can discriminate at late times after trauma between sites where flow has returned to near control levels from ischemia and sites where flow had never been greatly depressed. The hydrogen electrode technique measures flow at only a few sites, however, since use of multiple electrodes is technically difficult. These studies indicate that the hydrogen clearance method can provide an accurate index of the longitudinal heterogeneity of blood flow in a single region of white matter if a large enough series of animals is used. The antipyrine technique, on the other hand, permits exhaustive assessment of heterogeneity of flow, including multiple regions of gray and white matter, but only at a single time point per animal. Together, the techniques are complementary.

The differences between gray- and white-matter flows show clearly that techniques that measure whole-segment SCBF will cause misleading conclusions about blood flow changes. For example, gray-matter SCBF at the center of trauma one hour after trauma is greatly reduced, while white-matter flow is largely unaffected. In contrast to white matter, the gradient of gray-matter SCBF shows a sharply defined ischemic focus. These differences, in both the onset of ischemia and the longitudinal pattern of flow, suggest that gray and white matter are responding as if to injuries that are different in degree and character. Spinal cord gray matter acts as if it has undergone a sharp contusion with rapid, long-lasting effects, while white matter acts as if it sustained a blunt contusion with delayed and variable effects on blood flow. Small blood vessels in the gray matter are more easily broken by the impact than white-matter vessels as demonstrated by earlier studies and much greater hemorrhage is found in gray than in white matter. The physical structure of nerve bundles in white matter may endow them with more elasticity than gray matter neuronal cell bodies and surrounding glia, and thus the energy of injury may be dissipated with less total damage to white matter than to gray matter. Differences in flow are sometimes also found regionally within the white matter, as when ventral white-matter SCBF predominated, as well as longitudinally, where regions of near control white-matter SCBF were interspersed among regions of decreased flow. These patterns may only be accurately assessed with a technique that allows recording from relatively small regions of the cord. Thus it has been suggested that the antipyrine method be employed, at least qualitatively, in conjunction with the hydrogen clearance method, in order to aid in evaluating possibly heterogeneous blood flow.

Assessments of the effect of trauma dose on spinal cord edema indicate that the spread of post-traumatic edema is directly related to the amount of energy in the initial traumatic event. Trauma sufficient to produce a permanent paraplegia results in not only tissue damage in the area of impact, but an extension of labelled albumin and dextrans (indicating loss of blood brain barrier integrity) and an increase in tissue water rostral and caudal to the site of injury. In contrast, a lower trauma dose, which produces only transient paraplegia, is not followed by increased water or extravascular fluorescence outside the region of trauma. It is likely that the changes in tissue water content observed at the site of impact shortly after trauma are more closely related to the hemorrhage and necrosis which follow the trauma in that location and, therefore, do not reflect true edema. The extension of edema longitudinally in the white matter, after trauma of great magnitude, is likely to be associated with the development of tissue pressure gradients between the area adjacent to the injury site and areas more rostral and caudal. The one to two hour delay in spread, during the same period that pressure gradients are developing, would seem to reflect the time required to overcome the resistance to spread that may be conferred by the white matter.

Biomechanical studies of the vertebral column yield quantitative data on the sagittal translation and rotation between normal cervical vertebra under axial loads. Cervical traction is applied to normal subjects and the mean and standard deviation of displacement and rotation between adjacent cervical vertebra is calculated in the sagittal plane. These norms may ultimately serve to determine when abnormal motion occurs in pathological conditions of the cervical spine. The investigators suggest that a stretch test (controlled, monitored axial loading) of the cervical spine may be helpful in the determination of clinical instability.

Other studies at Yale are delineating neuraxis circuitry and neurochemical properties. There is now biochemical evidence for simultaneous activation of multiple locus coeruleus (noradrenergic) efferents, e.g., to the cerebral cortex hippocampus, cerebellum and spinal cord. The results support the hypothesis of simultaneous activation of diffuse efferents and the proposed modulatory role of the locus coeruleus.

Additional projects have explored changes in the somatopic map of the sensory-motor cortex following the transection of spinal dorsal roots. These studies reveal increased effectiveness of afferents from intact body segments in activating cells in the deafferented region. The latter changes are complete 30 weeks following deafferentation. Furthermore, there is the reaffirmation of widespread, but latent and ineffective afferent synapses throughout the somatosensory system of intact animals. Additional investigative projects include exploration of the sea lamprey as an experimental model for understanding spinal cord regeneration or non-regeneration in the vertebrate, and the urodynamics of the spinal-injured.

The Clinical Research Center grant at the Medical University of South Carolina is pursuing studies concerning the problem of acute spinal cord injury. This program combines clinical and experimental laboratory projects for elucidating the basic pathophysiology and electrophysiology of cord injury, and for the design and evaluation of new methods for the treatment of acute spinal cord injury. Laboratory animal studies are designed to yield information in the following areas: electrophysiology of the normal and injured spinal cord utilizing somatosensory evoked potential (SEP) techniques; spinal cord blood flow; focal alterations in metabolism of the spinal cord using autoradiographic techniques; ultrastructural changes in varying degrees of cord injury; biochemical factors in the pathogenesis of spinal cord and axonal injury; and the effects of various forms of experimental therapy on normal and injured cords.

Electrophysiological studies on the spinal cord have confirmed the origin of the SEP and new procedures for discriminant analysis of SEP are under development. These investigators have also raised the prospect of using far field potentials in the diagnosis of spinal cord and brain injuries. In addition glucose utilization within the normal and injured spinal cord is being explored through use of the 2-deoxy-glucose method.

Correlated neuropathological and biochemical studies are scrutinizing the role of calcium in the post-trauma interval. Using atomic absorption spectroscopy the investigators show a significant increase within the lesion area 45 minutes after injury and a four-fold increase at eight hours. Thereafter the calcium level remains relatively constant for 48 to 72 hours. Since calcium-activated proteases are present in the spinal cord, the high levels of calcium accompanying trauma could precipitate some measure of the myelin degradation observed following injury.

Clinical studies at MUSC entail intensive monitoring of patients with acute spinal cord injury using the technique of SEP in an Acute Spinal Cord Injury Treatment Unit. Work in the unit has shown that the presence or absence of a response to bilateral posterior tibial nerve stimulation is a reliable index of whether the spinal cord lesion is clinically complete or incomplete. This investigative group also has characterized a variety of spinal cord disorders (e.g., Anterior Cord Syndrome, Brown-Sequard Syndrome and Central Cord Syndrome). Finally, recent studies suggest that the SEP technique promises to be a very effective tool in the monitoring of cord function during reduction of spinal fracture dislocations in those patients with incomplete injury.

At New York University the Clinical Research Center for Acute Spinal Cord Injuries continues to exploit the most recent observations relevant to CNS trauma. The program is composed of fundamental and clinical studies.

The neurophysiological studies have been devoted to three lines of experimentation; 1) doing correlative neurophysiological monitoring of function in conjunction with other experiments on SCBF and biochemical analyses of injured spinal cords; 2) establishing rigorous criteria for interpreting both acute and chronic changes in SEP; and 3) measuring extracellular activities of potassium and calcium ions in injured spinal tissues. As a result of these studies in cats three important phenomena have been observed: 1) the absence of SEPs at the third hour after injury is not as grave a prognostic sign as previously reported by this laboratory; 2) treatment paradigms that ameliorate the post-traumatic ischemia preserve neurophysiological, as well as neurological function 24 hours after injury; and 3) a secondary loss of SEPs and deterioration of neurological function 1-4 weeks after injury is commonplace and does not rule out the possibility of eventual neurological improvement. These observations suggest that some of the symptomatology of severe contusion injury may be related not to irreversible dissolution of long tracts, but rather to physiological suppression of some morphologically preserved systems. Furthermore, they point to the possible presence of long-term injury processes, which have been only hinted at in the past, taking place days and weeks after contusion. These processes may not be limited to the contusion site; changes in both the proximal and distal cord may be responsible. An ultrasonic spinal injury model is now being tested to facilitate further studies in these areas, particularly with respect to SEP.

Studies of extracellular potassium and calcium in injured spinal tissues are using ion-sensitive microelectrodes. These experiments show that immediately after severe impact, extracellular potassium rises dramatically. These extraordinary levels of potassium, implicating drastic ionic derangements in the tissue, require 2-3 hours to return to normal. Correlations between local blood flow rates and the time course of potassium clearance from the extracellular space have been observed. These experiments documenting ionic derangements directly in tissue, indicate that contusion injury causes massive loss of selective cellular membrane permeability. Furthermore, the long time required for the clearance of potassium from the extracellular space suggests that either cellular pumping mechanisms are impaired or there is a continued cellular permeability to these ions.

Membrane permeability depends upon the membrane ion-pumping enzyme sodium-potassium adenosine triphosphatase (Na-K ATPase). Changes in the ATase have been observed, suggesting an alteration in its membrane lipid environment.

Biochemical studies have focused on the loss of membrane lipids, the appearance of free radical oxidation products of the membrane lipids, and prostaglandin profiles. The hypothesis currently under scrutiny is whether pathologic lipid-free radical reactions alter cell membranes and help to cause physiologic losses in neuronal function and in blood flow in the spinal cord. Iron and copper from extravasated blood, in areas of spinal cord trauma, initiate and catalyze these pathologic radical reactions. The secondary ischemia occurring at two hours after injury may add to the initiation and catalysis. Using model membranes, e.g., liposomes, as well as membranes from the spinal injured animal, the investigators have shown lipid oxidation as a result of free radical damage. Tissues from the spinal impact model show significant reductions in polyunsaturated fatty acids, arachidonic acid and docosahexaenoic acid by five hours after injury. At the same time cholesterol oxidation products become evident. Current efforts are directed at understanding the functions of natural occurring and therapeutic antioxidants, including ascorbic acid, glutathione, methylprednisolone, and naloxone.

A consequence of free radical damage may be inhibition of prostacylin, the aggregation of platelets and finally microcclusion of blood vessels. Thus the prostaglandins and related factors are to be assayed in injured tissue and in platelets. Determinations continue to be made of the effects of several putative therapeutic agents on post-traumatic ischemia, e.g., aminophylline, isoproterenol and naloxone.

Clinical research projects at NYU include continued participation in the multicenter spinal cord injury steroid treatment study (data processed through Yale University) and extension of SEP studies to all neurosurgical procedures involving manipulation of the spinal cord.

The Spinal Cord Injury Research Center at Ohio State University represents a fundamental approach to the biological manifestations of spinal cord injury. The physiological condition of the injured tissues is being assessed using oxygen and potassium microelectrodes, and initial studies suggest that the extracellular fields of the traumatized spinal cord are markedly altered.

The search for primary factors in the autodestructive pathophysiological process has turned from catecholamines and lysosomal enzymes to specific mitochondrial enzymes and plasma membrane Na-K ATPase, with reductions in the two latter parameters seen at fifteen and five minutes after injury, respectively. Efforts are ongoing to determine the mechanism of white matter injury after trauma. The possibility remains that enzymes inherent in the nervous system, e.g., plasmalogenase, lipases and phospholipases, cause a sequential degradation of plasma membrane. Among the breakdown products are arachidonate and related fatty acids. These may be converted to prostaglandins or thromboxanes, which in turn could cause further direct damage to neural and glial constituents and possibly help compromise the local circulatory system.

The peripheral nervous system is used as a model for understanding post-traumatic sequelae. For instance, studies of myelin associated lipids reveal that younger animals metabolize neural debris more rapidly during Wallerian degeneration than do older animals.

Finally, a number of investigators are studying the development, organization and function of various sensory and motor inputs to segments of the spinal cord. These studies should provide a sound foundation from which to approach the topics of regeneration and post-injury treatment.

Investigators at the University of Texas, San Antonio, using physiological, metabolic and neuropharmacologic approaches are engaged in a Program of Research in Spinal Cord Injury.

One series of studies is intended to delineate the connectivity between brain stem neurons, belonging to the vestibulo- and reticulospinal systems and the lumbosacral motoneurons. Studying cats and monkeys with intact and partially sectioned spinal cords, an effort is underway to distinguish reorganization processes from intrinsic reflex movements (e.g., spinal stepping) in recovery of locomotor function following cord lesions. Another study seeks the relationship between pharmacologic supersensitivity of the cyclic AMP system and the hyperreflexia which occurs as a result of spinal cord injury. Findings in this realm could lead to improved therapeutic interventions for the hyperreflexia and spasticity which accompany spinal cord injury.

The mechanisms responsible for the degradation of myelin following CNS injury remain unclear. The involvement of sphingolipids and sphingolipases in the degenerative process is a primary research focus. Although considerable research effort has been directed at the site of trauma, little is known of the consequences of the injury to other parts of the central nervous system. Regional metabolic concomitants of spinal shock and recovery and the consequences of long axon destruction are being followed using the 2-deoxy-glucose method of Sokoloff.

The National Acute Spinal Cord Injury Study is entering its final year and final phases. The study is a double blind randomized collaborative clinical trial originally involving seven spinal cord injury centers: Yale-New Haven Medical Center, New York University-Bellevue, Medical University of South Carolina, Ohio State University, University of Texas Medical Branch, University of Miami, and the University of Puerto Rico. The Riverside Hospital, Columbus, Ohio, and the Baylor College of Medicine, Houston, Texas have since been added to the program. Data collection started on February 1, 1979. The purpose of the study is to examine the efficacy of large doses of methylprednisolone in the early treatment of acute spinal cord injury. All eligible patients are invited to participate and those consenting are randomly assigned to standard or to large doses of methylprednisolone (100 mg. versus 1000 mg. respectively for 10 days). Neurological examinations are performed on these patients at six weeks, six months, and one year post injury. Differences in neurological function between the standard dose and high dose groups and the role of potentially confounding variables are examined. On the basis of patient intake and to achieve statistical significance the program will be extended into 1982. This will permit completion of the follow-up examinations on patients randomized through the latter part of 1981.

In addition to the Spinal Cord Injury Research Centers there are 14 (fourteen) individual research grants dealing with the spinal cord. These vary from basic anatomy, physiology and biochemistry such as: "Organization of Spinal Cord," "Electrophysiology of Spinal Cord Injury," and "Spinal Cord Lesions - Neurobiological Mechanisms," to clinical studies such as "Social Relations and Microecology of Paraplegics," "Evoked Spinal Response," and "Outcome Versus Emergency Care in Spinal Cord Injury."

IV. HEAD INJURY

Clinical studies in recent years illustrate increased survival rates for those severely head-injured patients treated in specialized CNS intensive care units. However, while mortality may be markedly reduced, restoration of the patients to near normal life-styles still leaves much to be desired. Thus the emphasis of the clinical programs is shifting significantly to a broad effort at delineating prognostic indicators of survival and non-survival, as well as the quality of life of the survivors. Research programs on the other hand are shifting to a cellular and metabolic level in order to determine the sequence of biochemical events related to injury.

The results of batteries of clinical, electrophysiological, biochemical and neuropsychological tests are being correlated using the reducing power of the computer to analyze copious data. Several years of effort will be required before the full impact of the effort is recognized. The findings will be particularly important with respect to future treatment regimens, in terms of future allocations of scarce clinical resources, and in the use of those resources to achieve the best possible clinical results.

An important feature of the latest approach to the CNS-injured patient is the increased emphasis placed on the functional aspects of other organ systems. Further recognition of the inter-relatedness of cardiopulmonary function, post-trauma nutrition, electrolyte balance and other factors suggests a potential for still further improvement in treatment and outcome following CNS injury.

Areas of fundamental interest continue to expand and thus basic problems associated with head trauma, e.g., ischemia, hypoxia, edema and increased intracranial pressure are under intense and diversified study.

Many of the problems of head injury are common to spinal cord as well, and are described in that section of this report. An exciting example, alluded to under spinal cord injury, is the effect of injury-induced free radicals on cerebrovascular blood flow. The cerebrovascular system may be severely compromised following head injury. One manifestation of the circulatory disturbance is reduced oxygen consumption rates of small pial vessels (observed _in vitro_). Arachidonic acid, presumably a derivative of injured neural tissue, is observed to lower pial vessel oxygen consumption. Since generation of free oxygen radicals from the metabolism of arachidonic may mediate the damage to the vessels, investigators at the Virginia Commonwealth University have attempted _in vitro_ amelioration of vessel injury. Through the combined addition of superoxide dismutase, an enzyme which destroys the superoxide anion radical by dismutation, and of catalase, an enzyme which destroys hydrogen peroxide, the effect of arachidonic acid on oxygen consumption is reversed.

Platelet aggregation is suggested as one of the deleterious sequelae to brain injury. Investigators at several institutions including the Richmond, Virginia, group are providing preliminary findings implicating prostaglandins as mediators of a clotting cascade effect. Therapeutic intervention to reverse this or similar processes would seem within the realm of possibility. There is an ever-growing mood within the research community that improved treatment for head injury will include drug cocktails designed to rectify the multi-faceted repercussions resulting from brain trauma.

The NINCDS supports five Head Injury Clinical Research Centers. These are located at the Virginia Commonwealth University, The University of Pennsylvania, New York University, Albany Medical College and The University of Texas at Galveston. Other NINCDS-sponsored activities include a program on cerebral edema at the University of California at San Francisco and an extensive clinical coma study at the University of Pittsburgh. The Institute supports another eleven individual research projects at various institutions in the United States.

V. CNS NEOPLASMS

The Stroke and Trauma research program in CNS Neoplasm is primarily related to basic and applied studies of the biologic events related to neoplastic growth. Investigators have studied the mechanism of catalysis and regulation of phosphotransferase enzyme hexokinase 1 and fructose 1,6-biphosphatase. Loss of this activity was demonstrated to be due to proteination of a single group on the enzyme. During the course of these investigations, scientist discovered that aluminum ions, not previously found or felt to play an important roll, did in fact provide intense inhibition in small concentrations. Thus studies of this process must be monitored closely for traces of aluminum.

Several studies have utilized cloned cell lines as a model to investigate the environmental stimuli and nutritive factors involved in such interactions and their biochemical events, the effects of protein phosphorylation on cultured cells and hormonally regulated responses, and the influence of nerve growth factor and NGF receptors on specific tumor cell lines. All of these studies are directed toward a better understanding of the basic biochemical events related to cell growth, regulation, heterogeneity and eventually the control mechanisms of tumor cells. Other groups are attempting to produce monoclonal antibodies of high specific activity which recognize molecules related to nervous system differentiation vs tumors. These antibodies will then be used to study the development of tumors with respect to the biochemistry of the antigens and the variability in biology and genetics of cells and antigens. During the past year, they have utilized two monoclonal antibodies from human neuroblastoma cells which have unequivocally identified neuroblastoma cells in bone marrow from neuroblastoma patients. Thus a sensitive method for determining small numbers of tumor cells (not ordinarily seen under the microscope) has been developed.

Other research has attempted to develop a series of diagnostic and seriologic tests which will permit the diagnosis, evaluation and severity and rate of progression of nervous system diseases and the results of cellular damage. Using somatic cell hybrids of human and mouse neuroblastoma cells the chromosomal location for the hybrid tyrosine hydroxylase-encoding gene is being determined. The significance of this finding would be the determination of whether genes that are functionally linked may also be linked genetically, i.e., may reside on the same chromosome. Other investigators are determining the specific functions of methyltransferase in murine neuroblastoma or the appearance of neurotransmitter enzymes and the relationship of neural morphology to specific neuroblastoma clones. The adhesion (or lack thereof) of tumor cells is an important variable related to mobility and metastatic potential. Studies have been carried out which show how neuronal cells adhere and the specific interaction of neurites with the substratum in which they exist.

Radiosensitizers are drugs which potentiate the effects of radiotherapy. The clinical use of nitroimidazole hypoxic cell sensitizers is limited by their neurotoxic side effects. The toxicity and pharmacokinetics of misonidazole and related radiation sensitizers, the dose response curve, the contribution made by electron affinity and lipophilicity, and the specific locus of the neurotoxic lesion are being determined. No specific preferential location for C^{14} labeled misonidazole within the CNS could be determined although brain stem nuclei appear histologically to be most affected. Further investigation into this important area is being carried out.

Many experimental models of intracerebral tumor have been developed; however, the true relationship of these models to the human process has not always been made. Research has examined the distribution and leakage of horseradish peroxidase (HRP) in a variety of different model systems, showing, in preliminary data, that human glioblastoma cell lines studied in athymic (nude) mice are much more similar to ASV model than the 9L intracranial tumor. Autoradiographic and other studies related to experimental model systems will be undertaken. The growth and treatment of human gliomas are made possible in the athymic (nude) mouse by virtue of the fact that this model does not reject the tumor line. A new young investigator is attempting to determine dose effect relationship of therapeutic agents, the growth kinetics and tumor morphology during serial passage in this model.

A major problem in tumor treatment relates to cerebral edema and the mechanisms of CSF solute exchange. One group of investigators is studying the structural and functional mechanisms involved in protein synthesis and secretion by choroidal epithelial cells while another group is examining the biomechanics of the edematous process, particularly the spread of fluid by bulk flow.

Additional studies are being undertaken in ultrasonic brain imaging, quantitative CT scan analysis of water and tissue alterations associated with hydrocephalus, and intracranial pressure relationships secondary to tumor.

STP has an interest in and intends to continue its activity in basic and applied research in the treatment of malignant brain tumors. It is hoped that increased grant activity can be stimulated which is supplementary to on-going research projects and which has specific relations to the goals of NINCDS.

VI. NEURAL REGENERATION AND PLASTICITY

Research into neural regeneration and plasticity is characterized by an expanding conceptual approach and an ever widening data base. Recent conferences attended by interested investigators have begun to take on a prospective as well as retrospective flavor. The broad range of on-going scientific inquiries and the multidisciplinary approaches used are only partially summarized here.

Investigators at the University of California at San Diego and University of Utah are characterizing the various macromolecular agents derived from glia and target organs which control in vitro survival of cholinergic and other neurons, as well as the trajectory of neurite growth. At UCSD a new ciliary neuronotrophic factor (CNTF) and substances in conditioned media are currently being characterized with regard to sources, molecular and immunochemical properties, neuronal target spectrum, neuronal effects in vitro and the roles they play in vivo. Since different classes of neurons may depend on specific trophic factors for their maintenance, growth, functional activity, and possibly repair, these studies are of theoretical and practical importance to neurobiologists and clinical neurologists.

At the University of Utah earlier work has shown that specifically conditioned medium contains two different agents, each of which dramatically stimulates axon outgrowth from parasympathetic neurons in vitro. One of these agents, a substratum conditioning factor, must bind to the culture substratum to induce neurite outgrowth, apparently by providing adhesion sites for neuronal filopodia on the substratum. The second factor, which can be readily separated from the former, promotes the long-term survival of parasympathetic neurons in culture. Recent studies show that if the substratum conditioning factor is laid down in a defined pattern on the culture substratum, elongating axons will closely follow this pattern. Thus, when axons approach the borderline between an area coated with the factor and an area from which it is absent, the growth cones of such axons fail to cross the border; rather they turn in order to remain in contact with the factor-coated substratum. This suggests that the factor may be related to those components of the in vivo substratum which direct axon outgrowth, and also that an implant coated with this factor might be used to guide regenerating axons. Related work demonstrates that the microexudate deposited by embryonic heart cells directly onto their culture substratum will support rapid neurite outgrowth. Thus, the heart cells not only release a substratum conditioning factor into their culture medium as previously shown, but they also deposit material with a similar axon growth promoting activity directly onto their culture substratum. Thus, it is becoming more probable that this factor represents some component of the cell surface or extracellular matrix which is released in culture. The work on the substratum factor(s) provides important insights into how the environment provided by nonneuronal cells is able to support and direct axon outgrowth in vivo. This information is related both to an understanding of the genesis of neuronal connections during embryonic development and to the manipulation of axon outgrowth during neural regeneration.

Researchers at the Cornell University Medical College are engaged in an analysis of the factors that contribute to successful regeneration in the goldfish optic system, and in the search for means of enhancing regeneration in this system. Findings of this nature may then be applied to systems that normally regenerate poorly or not at all. In related studies it has been shown that a block of physiological (electrical) activity for up to three days has little effect on slow axonal transport; block of protein synthesis in the cell body immediately prevents the advance of transport; and in axons isolated from their cell bodies, transport continues for 24 hours. The importance of Ca++ in outgrowth of regenerating goldfish optic axons has been demonstrated by showing that outgrowth is enhanced when the Ca++ ionophore A 23187 is injected into the eye or locally applied at the site of an optic nerve lesion. The enhanced outgrowth is evident from an accelerated rate of recovery of reflex responses to visual stimulation. Also observed is increased axonal transport of ^{45}Ca during regeneration.

A research program on neural transplants is ongoing at the University of Rochester. Hypothalamic tissue containing vasopressin neurons from normal 17- and 19-day old rat fetuses is transplanted into the third ventricle of adult Brattleboro rats. The latter commonly exhibit excessive thirst and inability to concentrate urine. The grafts result in pronounced antidiuretic influences with water consumption decreasing and urine osmolality increasing in the host animals. The results indicate that the transplanted neurons can make appropriate and functional connections in the host brain, with vasopressin being synthesized and released into the systemic circulation.

Related studies at UCSD focusing on transplantation of neural tissue have addressed 1) the transition zone between the implant of embryonic CNS tissue and the lesioned surface of the adult recipients CNS; 2) the effect of a post-lesion time-delayed implantation; and 3) competition between cholinergic axons of implants and the anomalous sprouts of the sympathetic nervous system in reinnervated regions of the CNS. The results indicate that axons from embryonic implants are not able to invade the mature postsynaptic CNS environment of the adult recipient along the entire zone of fusion between the two tissues. Inaccessible regions are those covered by pial cells or containing densely myelinated fiber tracts. The ability of embryonic cholinergic axons to reinnervate their appropriate target sites in the adult hippocampus, even though there is a six-week delay from the time of the initial lesion to the implantation of the embryonic tissue, is particularly important, since it indicates that a considerable time period can elapse after the initial lesion without preventing the reinnervation of a target site by the appropriate afferents. Thus, considerable synaptic reorganiation can occur within the denervated postsynaptic target without preventing the ingrowth of a lost specific afferent. Another important finding is the observation that at least some anomalous (and perhaps detrimental) innervations that arise as the result of an injury to the adult CNS can be retracted by reintroducing a proper afferent to the injured region. However, there appears to be a critical period during which the anomalous innervation can be retracted. Once this time period has elapsed, the anomalous fibers appear to be "stabilized" and not retracted. A further understanding of the competition between intrinsic afferents and anomalous projections to an injured brain region should have important implications for understanding the plastic and healing responses which occur within the adult human CNS following injuries and neurosurgical interventions.

An objective of an investigator at the University of Maryland is to determine whether grafts of fetal spinal cord tissue can stimulate axonal elongation through a site of injury in the adult spinal cord. The results of recent studies, however, have questioned whether grafted fetal spinal cord tissue can survive and differentiate after being transplanted to a lesion site in the CNS. Therefore, it was necessary to define the extent to which segments of the immature spinal cord survive and mature under appropriate neural tissue grafting conditions. For this purpose, pieces of the spinal cord from rat fetuses were implanted into either the ventricular system or choroid fissure region of the adult brain. Both of these implant sites have been shown to be favorable environments for the differentiation and long-term maintenance of other neural tissue grafts. The findings demonstrate that the spinal cord, depending upon the age of the donor, is capable of extensive differentiation and prolonged survival after transplantation. In addition, distinct regions of gray matter develop in these grafts, and structural contiguity with the host brain is established. In silver-stained histological preparations, axons are often seen traversing the host-graft interface. Immunocytochemical and ultrastructural examination of the transplants also indicate that no distinct glial barrier is formed at the interface. This result suggests that the presence of CNS tissue at the site of injury may retard or prevent the development of a glial scar. Investigations are currently underway to test this hypothesis. Further studies are planned to determine the viability of grafted tissues placed in lesions of the spinal cord and the response of the lesioned cord to the graft.

Investigators at Ohio University, the University of California at Los Angeles and the University of Texas, San Antonio, continue studies on spinal reflexes, spinal conditioning processes and spinal fixation phenomenon. While the spinal cord is considered by many to have much simpler circuitry and learning capacity than the brain, the intricacies of its functional capability remain relatively obscure. Nevertheless, the several investigative groups continue to explore intrinsic functions of the cord, some of which may serve as latent resources in rehabilitation from spinal cord injury.

At the University of Michigan, investigators are seeking markers of nerve cell response to axotomy and identification of those steps which are necessary for axon regeneration. Markers of cell response discerned thus far include tubulin labelling and increased tubulin mRNA, increased nucleotide kinases, and increased ornithine decarboxylase. Which of these changes may be necessary for axonal regrowth has not yet been established.

Research teams at Childrens Hospital, Boston, Washington University, St. Louis, Stanford University and elsewhere are examining the neurite guidance potential of a number of synthetic and biological substances. The most promising substrates are being used to study basic biological processes associated with axonal elongation and trajectory *in vitro* and to devise neural prostheses for bridging gaps in the injured peripheral and central nervous systems.

VII. PAIN

Investigators at the University of Washington are combining two experimental techniques, brain evoked potentials and sensory decision theory, to assess pain perception in patients suffering from acute and chronic pain. In the few months since the new program project grant was awarded, this group has established a computer-based system for collection, storage, and analysis of evoked potentials from multiple scalp sites in human subjects. Work has begun on a study of the neurophysiology and neuropharmacology of pain in the rhesus monkey using behavioral methods (most notably those of signal detection theory) identical to those employed in humans.

During the past few months 64 acute, 34 chronic, and 4 tic douloureux patients have been recruited for a study to document the differential in psychological and social characteristics of acute and chronic pain patients.

Although precise epidemiological data are not available on headache, they are thought to constitute a sizable health problem. Two primary procedures utilized in headache treatment are relaxation and biofeedback training. A study is in progress at Midwest Research Institute to test the efficacy of behavior treatment interventions on vascular headache of the migraine type, muscle contraction headache and combined vascular and muscle - contraction headache.

Migraine headache is a public health problem involving several million patients per year for which no reliable treatment exists. Although a wide spectrum of drugs are available, many are associated with medical risks and few, if any, have been evaluated in a controlled clinical trial. A comparative trial of amitriptylin propanolol, and placebo in a population of patients with severe or disabling headaches is underway at Kansas University Medical Center. Patients are being tested pharmacologically to evaluate response or toxicity to concurrent plasma drug concentration. A unique feature of this study is that it is designed to provide data on the characteristics of the patients most likely to respond to either drug as well as on the comparative efficacy of the two drugs. A part of the study is concerned with serotonin uptake by platelets, since there is much evidence implicating platelet abnormalities in this condition.

The use of positron emitting radionuclides incorporated in opiate agonist and antagonist molecules as well as endorphins in conjunction with positron emission tomography makes possible the probing of ligand-receptor interrelationships in the whole animal. The availability of opiate receptor specific compounds such as ^{11}C diprenorphine offers an unparalleled opportunity for the expansion of our knowledge of the system within the brain which is important for pain control, its interaction with catecholamine systems, and the effects of electrical stimulation of the nervous system upon this pain control system.

CONTRACT NARRATIVE
Stroke and Trauma Program, NINCDS
October 1, 1980 -- September 30, 1981

Institutions

University of Rochester (N01-NS-8-2385)
North Carolina Heart Association (N01-NS-8-2386)
University of Oregon Health Sciences Center (N01-NS-8-2387)

Title: Comprehensive Stroke Center

Contractor's Project Directors: John H. Feibel, M.D. (Univ. of Rochester)
Paul E. Hirschauer (North Carolina Heart Assoc.)
Frank M. Yatsu, M.D. (Univ. of Oregon)

Current Level of Support: $ 73,300 (UR)
150,000 (NCHA)
50,000 (UOHSC)

Objectives: The objectives of these centers are to:

a. Conduct a program of applied clinical research in which fundamental advances are utilized in the development of specific approach for the prevention, diagnosis and mangement of cerebrovascular disorders.

b. Develop integrated and coordinated community resources to evaluate the results of research on the prevention, diagnosis, and treatment of cerebrovascular disorders.

c. Demonstrate to physicians, other professionals and the public, by a broad public education program, the significant advances in cerebrovascular research and management.

Major Findings and Proposed Course:

1. North Carolina Heart Association

The Comprehensive Stroke Center Program in North Carolina is engaged in a community based effort to improve the in-hospital care of stroke patients and to provide more extensive post-hospitalization services. It is being conducted in three groups of counties in the southeast portion of the state, an area which is underserved by sophisticated medical expertise. By measuring the outcome of stroke patients in these three different groupings in a before and after algorithm, the effect of the program is being evaluated. All hospitals in 15 counties are now collecting data on stroke patients. The intensive treatment program has been implemented in two groups of hospitals with the third group scheduled for the Fall of 1981. Follow-up data are being collected by Home Health Agencies in the 15 counties after the patient has been discharged from the hospital. Stroke teams and other allied and medical health personnel are continuing to receive professional education from staff of the Comprehensive Stroke Program. Community Stroke Councils have been organized to develop and implement stroke-prevention activites.

2. University of Rochester Stroke Center

This center is located in Monroe County, New York, the major city of which is Rochester. It includes all the community hospitals and health services with the focus at Strong Memorial Hospital. The benefits of the program are being seen in terms of increased physician and patient interest as well as an increase in cooperation from health care professionals dealing with stroke patients. The staff is continuing their outreach into nursing homes, hospitals, and community agencies on behalf of stroke patients.

3. The University of Oregon Health Sciences Center

The Comprehensive Stroke Center in Oregon has been organized around four projects: Education, Epidemiology and Preventive Medicine, Clinical Research, and Rehabilitation. Currently the emphasis is on the rehabilitation and clinical research aspects. Stroke rehabilitation teams have been organized by the Center to work in rural locales which lack resources and trained personnel. They are providing rehabilitation for stroke patients in the areas of nursing care, and physical and occupational therapy. Protocols for the treatment of acute stroke with barbiturates and aminophylline have been developed and implemented. Studies on cognitive and neuropsychological defects associated with stroke are continuing.

Significance to NINCDS Program and Biomedical Research: As research in the Stroke Clinical Reseach Centers has progressed, questions have arisen regarding the applicability of their efforts. Do any of the techniques developed at a particular clinical research center reach the surrounding community hospitals? If so, does their application there produce the same results as it does at the Center? Does the presence of a Center affect the distribution of care of the stroke community? Does the care given in the Center affect mortality or morbidity for a given type of stroke? Will intensive rehabilitation efforts help in some cases? The Comprehensive Stroke Centers are attempting to find answers to these questions.

Proposed Course: The three Centers have developed somewhat independent programs with a certan degree of overlap. During the third year the collection and analysis of patient data have been done in accordance with guidelines established jointly by the three Centers.

Contractor	Termination Date
University of Rochester	6/28/82
North Carolina Health Association, Inc. (now Am. Heart Assoc., N.C. Affiliate, Inc.)	5/31/82
University of Oregon Health Sciences Center	6/14/82

The completion of this work and the publication of its results is expected during FY 81-82 and is provided for by phase-out funding.

CONTRACT NARRATIVE
Stroke and Trauma Program, NINCDS
October 1, 1980 -- September 30, 1981

Institutions

University of California, San Diego (N01-NS-9-2312)
Albert Einstein College of Medicine (N01-NS-9-2313)
University of Texas Medical Branch (N01-NS-9-2314)

Title: Establishment of a Comprehensive Central Nervous System Truama Center

Contractor's Project Directors: Lawrence Marshall, M.D.
Kamran Tabbador, M.D.
Ralph F. Frankowski, Ph.D.

Current Annual Level of Support:	
$484,300	(UCSD)
538,900	(AECM)
443,200	(UTMB)

Objectives: The purpose of this program is to evaluate the availability and the efficacy of the care of patients with CNS trauma, and to develop guidelines for optimal care of these patients in the setting of their community resources. In conjunction with these broad goals, specific objectives will be to:

1. Develop coordinated community resources by means of which developments in CNS trauma research can be evaluated on a community basis.

2. Foster clinical research on improved diagnosis and treatment of patients with CNS trauma.

3. Bring results of research on CNS trauma rapidly and effectively to the general community and especially to those segments of the community with a high incidence of CNS trauma.

It is hoped that such a center could serve as a general guide to the development of improved facilities for patients with CNS injury in other communities with similar geographical and population characteristics.

Major Findings: The epidemiological and data collection and processing aspects have been further refined in an effort 1) to capture the most relevant information, 2) to allow comparable cumulative data to be derived from the several trauma centers, and, 3) to enable the most promising areas of clinical investigation to be explored. There has been further integration of regional hospital networks for referral of patients and data. Regional emergency services are being categorized and enhanced interactions fostered. The centers are working toward the development of general community awareness of the program and its goals. To help achieve the latter, several community advisory committees have been organized or are undergoing organization.

Significance to NINCDS Program and Biomedical Research: A survey of CNS trauma in the United States revealed approximately 400,000 new cases of head injury, severe enough to be hospitalized. Approximately one half of these cases were 24 years old or younger. Due to the youth of those incapacitated, the impact on national health and productivity is evident. Because of this, the NINCDS has had special interest in the problem of CNS trauma, and is supporting research, both in basic studies aimed at clarifying the pathophysiology of brain and spinal cord injury and in clinical studies designed to improve diagnosis and treatment, particularly in the period immediately following the injury. Through its programs of head injury and spinal cord injury research, information important to patient care is being obtained. New diagnostic techniques and new forms of treatment are being evaluated in specialized clinical research units. In view of the increasing amount of research in this field, it is now appropriate to evaluate this new information at the community level and to contribute to its utilization.

Proposed Course: It is expected that at least three years of support will be required to permit the acquisition of data, the evaluation of clinical interventions, and the establishment of fully operational trauma centers that can serve as research-service models for other communities.

☆U.S. GOVERNMENT PRINTING OFFICE: 1982-361-132:542

5017

NIH Library, Building 10
National Institutes of Health
Bethesda, Md. 20205

DATE DUE

GAYLORD
PRINTED IN U.S.A.

LIBR
Amazing
Amazing
http://nihlibrary.nih.

10 Center Drive
Bethesda, MD 20892-1150
301-496-1080

NIH LIBRARY
4 0146 9013

WERT
BOOKBINDING
MIDDLETOWN PA
SEPT. 82
We're Quality Bound

NIH LIBRARY
3 1496 00186 8291